

**STUDIES TOWARDS THE SYNTHESIS OF THE MARINE
METABOLITE OCTALACTIN-A**

Garnet E. Howells

Department of Chemistry
University of Edinburgh
January 1999



*For my parents, Sheila and Gordon
and for Emma*

ACKNOWLEDGEMENTS

I should like to record here my gratitude to Dr Alison N. Hulme, who supervised this work, for her wise direction, mature advice and encouragement throughout the project and for the final checking of this manuscript.

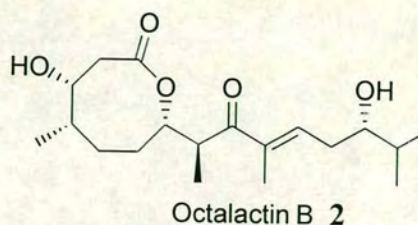
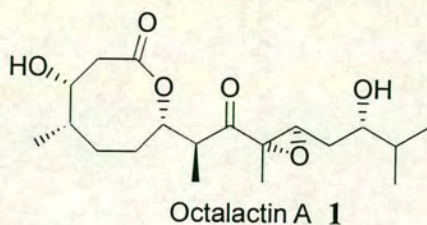
I am extremely grateful to Craig Jamieson for the initial proof-reading of this manuscript and for his endless humour over the past two years. I would also like to express thanks to the all of the technical staff of the Chemistry Department who have been of great assistance in one way or another over the last 3 years. In particular, John Millar and Wesley Kerr who ran 250 and 200 MHz NMR for me and Hewage for his superb work on the 600 MHz machine, all of whom have run spectra (often at short notice) as well as friendly, efficient services.

Thanks also go to the many people, friends and colleagues, who, over the past 3 years, have helped make it a most memorable time: Charles Montgomery (Burns) or *Mondo* for his entertaining wit and Christmas jingles, all the members of labs 54, 55, and the lab 29/34 select (you know who you are) for 'social outings' and the numerous friends I have made in and out of the Department during my time at Edinburgh.

Finally Emma, for your love and laughter, without which would have made the end unbearable.

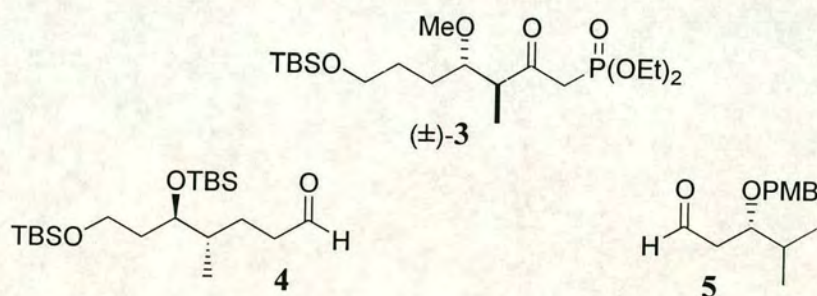
ABSTRACT

Studies towards the synthesis of the two novel eight membered ring lactone natural products, the cytotoxic octalactin A **1** and octalactin B **2**, will be described.



The first part of this thesis discusses the methodology developed for the potential application to a total synthesis of **1** and **2**. The key steps include; a boron mediated *anti* aldol coupling, an *E*-selective Horner Wadsworth Emmons coupling to give a tri-substituted double bond and a novel samarium-based cyclisation to produce several simple octalactin analogues containing unsubstituted rings (**Chapter 2**).

The second part of this thesis describes an extension of the methodology developed to the stereoselective synthesis of racemic **3**, a key fragment in the synthesis of the polyketide halichondramide (**Chapter 3**).



Finally, the third part of the thesis outlines a synthetic route towards the octalactins based on the previously developed methodology. This includes the asymmetric synthesis of the two major aldehyde fragments **4** and **5** (**Chapter 4**).

CONTENTS

DECLARATION	I
ACKNOWLEDGEMENTS	II
ABSTRACT	III

CHAPTER 1:	INTRODUCTION	1
1.1	Medium Ring Lactone Natural Products	1
1.2	The Octalactins	3
1.3	Asymmetric Boron Aldol Reaction	8
	1.3.1 Relative Stereocontrol	8
	1.3.2 Absolute (anti) Stereocontrol	12
1.4	The Acetate Aldol Reaction	14
	1.4.1 Selectivity in the Boron-Mediated Acetate Aldol	14
	1.4.2 Recent Advances in the Acetate Aldol Reaction	15
1.5	The Reformatsky Reaction	19
	1.5.1 The Chromium-Mediated Reformatsky Reaction	20
	1.5.2 Asymmetric Reformatsky Reaction	22
1.6	The Horner Wadsworth Emmons (HWE) Reaction	23
1.7	Samarium Diiodide	25
	1.7.1 The Tishchenko Reaction	26
	1.7.2 The Evans-Tishchenko Reaction	27

CHAPTER 2:	RESULTS AND DISCUSSION PART 1	30
------------	-------------------------------	----

MODEL STUDIES

2.1	Retrosynthetic Analysis of the Octalactins	32
2.2	Synthesis of Unfunctionalised Aldehydes	35
	2.2.1 Monoprotection of Symmetrical Diols	35
	2.2.2 Oxidation of Protected Diols	36
2.3	Anti Aldol Approach to the C(7)-C(8) Bond Connection	38
	2.3.1 Thioester Methodology	38
	2.3.2 Confirmation of Stereochemistry	41
2.4	Carbon Backbone Extension	42
	2.4.1 Thioester Displacement	42
	2.4.2 Horner Wadsworth Emmons (HWE) Coupling	46
2.5	Approach to the Cyclisation	49
	2.5.1 Deprotection of HWE adducts	49
	2.5.2 Oxidation	51

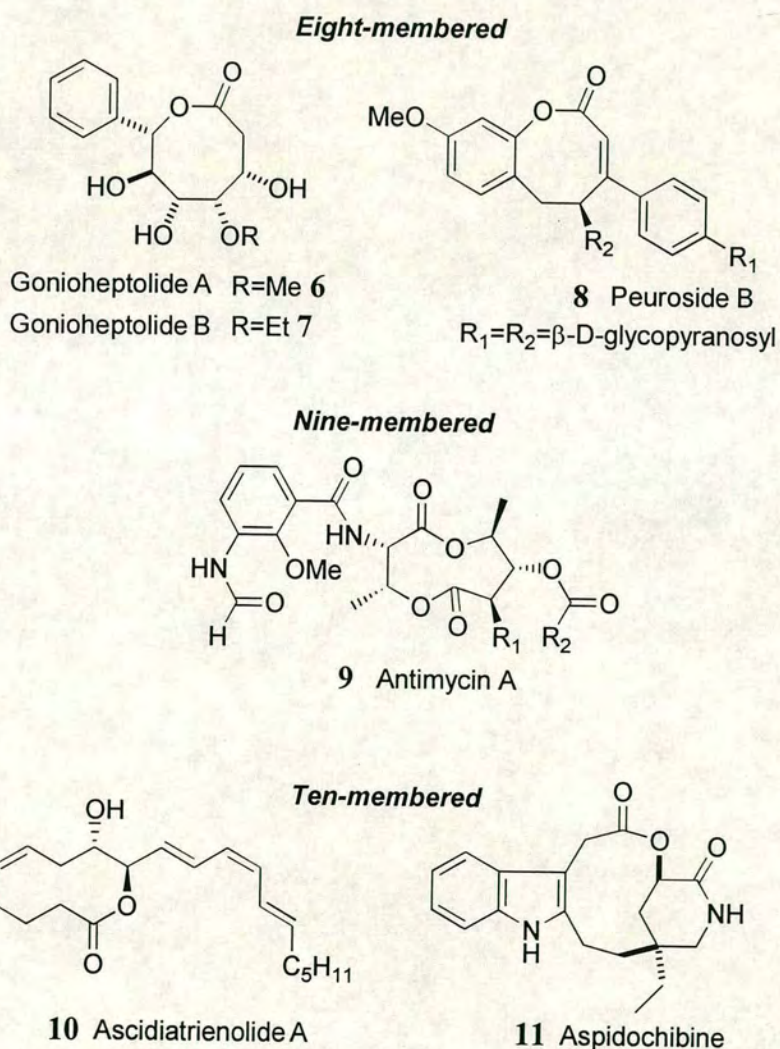
2.5.3	<i>Selective Oxidation</i>	52
2.5.4	<i>Evans-Tishchenko reactions</i>	54
2.5.5	<i>Intramolecular Evans-Tishchenko Cyclisation</i>	56
CHAPTER 3:	RESULTS AND DISCUSSION PART 2	62
	<i>SYNTHESIS OF THE C(29)-C(35) SECTION OF THE HALICHONDRAMIDE BACKBONE</i>	
3.1	Development of the Methodology	62
3.2	<i>Anti Aldol Coupling</i>	64
3.3	Thioester Displacement	67
CHAPTER 4:	RESULTS AND DISCUSSION PART 3	69
	<i>TOWARDS THE TOTAL SYNTHESIS OF THE OCTALACTINS</i>	
4.1	Synthesis of Aldehyde 5	69
4.1.1	<i>Acetate Aldol Coupling</i>	71
4.1.2	<i>Auxiliary Cleavage</i>	74
4.1.3	<i>PMB protection</i>	76
4.1.4	<i>Oxidation</i>	77
4.2	Synthesis of Aldehyde 4	79
4.2.1	<i>Epoxidation</i>	79
4.2.2	<i>1,2 Diol Formation and Periodate Cleavage</i>	80
4.2.3	<i>Acetate Aldol Approach to the C(3)-C(4) Bond Formation</i>	82
4.2.4	<i>The Asymmetric (Cr-Mediated) Reformatsky Reaction</i>	86
4.2.5	<i>Reformatsky Approach to the C(3)-C(4) bond formation</i>	88
4.2.6	<i>Ozonolysis</i>	91
4.3	Anti aldol Approach to the C(7)-C(8) Bond Formation	92
4.3.1	<i>Auxiliary Synthesis</i>	92
4.3.2	<i>Anti Aldol Coupling</i>	93
4.3.3	<i>Anionic Displacement</i>	95
4.3.4	<i>HWE Coupling: Construction of the C(10)-C(11) Bond</i>	98
4.3.5	<i>Deprotection of the HWE Adduct</i> 100
4.3.6	<i>Selective Oxidation</i>	102
4.3.7	<i>Evans-Tishchenko Cyclisation</i>	102
4.3.8	<i>Alternative Catalysts for the Evans-Tishchenko Reaction</i>	105
4.3.9	<i>Conclusions</i>	106

CHAPTER 5:	EXPERIMENTAL PROCEDURES	108
5.1	General Experimental	108
5.2	Experimental for Chapter 2	111
5.3	Experimental for Chapter 3	151
5.4	Experimental for Chapter 4	157
	<i>Selected ^1H and ^{13}C NMR spectra</i>	199
<i>REFERENCES</i>		201
<i>APPENDIX</i>		208
<i>PUBLICATIONS</i>		216
1. Hulme, A. N.; Howells, G. E. <i>Tetrahedron Lett.</i> 1997 , 38, 8245		216
2. Hulme, A. N.; Howells, G. E.; Walker, R. H. <i>Synlett</i> 1998 , 828		222
<i>ABBREVIATIONS</i>		225

CHAPTER 1

1.1 MEDIUM RING LACTONE NATURAL PRODUCTS

Medium ring lactones (ring size eight to eleven) have become an important feature in organic chemistry as they are contained in an increasing number of biologically active natural products.¹ Several of this class of natural products are depicted in **Scheme 1**.



Scheme 1 Selected medium ring lactone natural products

Due to the challenge of synthesis[†] and biological activities reported for this class of natural product there has been a large degree of synthetic interest in this area.¹ A few examples of biologically active medium ring lactone natural products are discussed briefly in this section.

In 1993, two eight-membered ring lactones **6** and **7** (**Scheme 1**) were isolated from *Goniothalamus giganteus* (Annonaceae) and both showed significant *in vitro* toxicity towards the cell lines of a variety of human carcinomas (*e.g.* **6**, IC₅₀ = 4.25 µg/ml towards A-549 (human lung carcinoma), **7**, IC₅₀ = 6.91 µg/ml towards HT-29 (human colon adenocarcinoma)).²

Peuroside B **8** (**Scheme 1**), as well as the related Peuroside A, both aromatic *O*-glycosides, were isolated recently from the roots of *Pueraria lobata* (Ohwi), the crude isolate of which is one of the most important oriental drugs.³

The Antimycins, a mixture of fermentation products, were first isolated from an unidentified strain of *Streptomyces* as early as 1949 but have been of significant interest recently. Five families (R₁ and R₂ as a variety of alkyl chains) have been well characterised and Antimycin A **9** (**Scheme 1**) has been shown to have interesting antibiotic properties.⁴

Ascidiatrienolide A isolated in 1989 from the marine derived *Didemnum candidum*, was recently established by Holmes as being the ten-membered lactone[‡] **10** (**Scheme 1**). The crude extract from *Didemnum candidum* exhibits strong *in vitro* inhibitory activity towards phospholipase A₂ and the activity is presumed to arise from a compound similar to **10**.⁵ Aspidochibine **11** (**Scheme 1**), another ten-membered lactone and new alkaloid was isolated in 1991 from the medicinal plant *Aspidosperma quebracho blanco* (Schlect).⁶ The extracted bark from which this

[†] The preparation of medium ring lactones has been a challenging topic for a long time due to the negative entropy required for the generation of these highly strained ring systems.¹

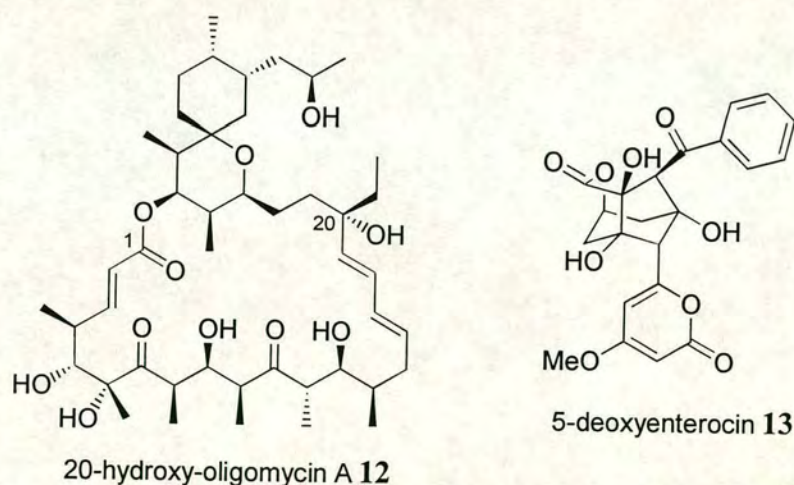
[‡] This compound was originally thought to be the corresponding nine-membered lactone, containing one less methylene unit in the ring and an extra methylene in the alkyl side chain.

natural product was isolated is used for the treatment of bronchial asthma in South America.

Only a limited number of eleven-membered lactone natural products are known and of these very few show any significant biological activity.

1.2 THE OCTALACTINS

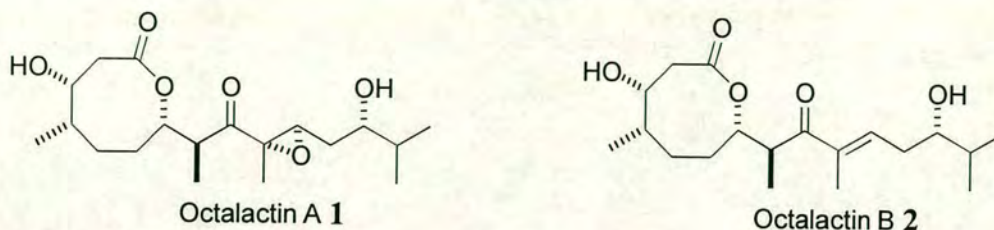
In 1991, Fenical and Clardy isolated an unidentified *Streptomyces* from the surface of a gorgonian octacoral of the genus *Pacifigorgia* sp. from the Sea of Cortez in the Gulf of California.⁷ The isolate (PG-19) produced a series of, thus far undescribed, metabolites possessing varying cytotoxic and antibiotic properties. Of these, the 20-hydroxy derivative of oligomycin A **12** and the 5-deoxy derivative of enterocin **13** showed comparable antibiotic properties to those of their parent molecules (**Scheme 2**).⁸



Scheme 2 Selected metabolites of extract PG-19

This organism also yielded, after repeated ethyl acetate extraction and chromatography, two novel eight-membered lactone ring, C-19 ketones, octalactin A **1** and octalactin B **2** (**Scheme 3**). The relative stereochemistry of octalactin A was

determined by X-ray crystallographic methods to be **1** and analysis of the ^1H NMR data showed octalactin B to be the corresponding C(10)-C(11) olefinic homologue.



Scheme 3 Structures of octalactin A and octalactin B

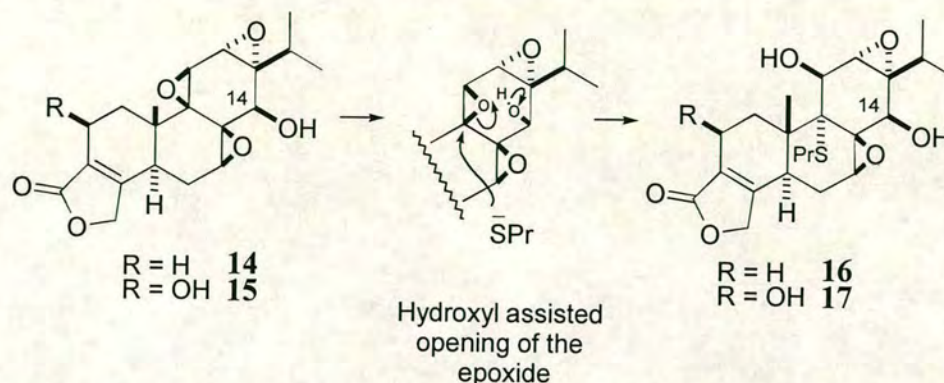
The octalactins contain rare 8-membered saturated ring lactone functionalities and octalactin A was reported to possess potent *in vitro* cytotoxicity against B16-F10 murine melanoma ($\text{IC}_{50} = 7.2 \times 10^{-3} \mu\text{g/ml}$) and HCT-116 human colon tumour cell lines ($\text{IC}_{50} = 0.5 \mu\text{g/ml}$).⁷

Octalactin B **2** differs from octalactin A **1** only slightly, having a double bond at C(10) in place of the epoxide, which suggests that the epoxy ketone functionality is an essential requirement for its cytotoxicity.

Through biomimetic studies done on antileukemic triptolides, Kupchan has hypothesised that the hydroxyl assisted attack by sulphur nucleophiles on an epoxide moiety $\beta\gamma$ to a hydroxyl group may mimic the mechanism by which the triptolide class of antileukemic agents exert their biological activity.⁹ Triptolide **14** and triptolide **15** were treated with an excess of propanethiol⁹ in phosphate buffer to give the corresponding ring opened products **16** and **17** respectively. It should be noted that the corresponding C(14) epimer of **14** does not react, suggesting that the relative epoxide/hydroxyl stereochemistry shown is important for the activity. This assumption is confirmed by the reduced activity of this homologue ($\text{IC}_{50} = 7.6 \times 10^{-2}$

⁹ A similar biomimetic approach has previously been used to demonstrate the activity of the tumour inhibitor, jatrophone which inhibits DNA-dependant RNA polymerase from *Escherichia coli* with concomitant reaction of enzyme SH groups.¹⁰

$\mu\text{g/ml}$) *c.f.* **14** ($\text{IC}_{50} = 1.7 \times 10^{-3} \mu\text{g/ml}$) towards L-1210 murine lymphoid leukaemia cell lines.⁹



Scheme 4 *Hydroxyl assisted biomimetic epoxide ring opening*

It is therefore possible that the activity of the octalactin extract is dependant on this structural motif but this has yet to be determined.

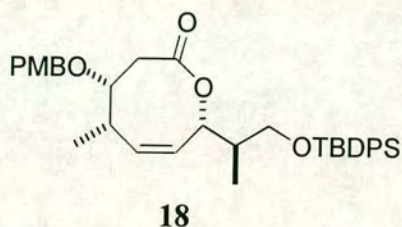
A recent total synthesis by Buszek has found a synthetic sample of octalactin A to be inactive towards L-1210 murine lymphoid leukaemia cell lines. It is not all that surprising that the synthetic material was found to be inactive as this assay was conducted on a different type of cell line to that tested by Fenical. It is well known that certain compounds exhibit highly differential cytotoxicities *i.e.* one compound may inactive towards one cell line but highly active towards another.¹¹ Taxol, for example, is almost inactive against leukaemias but is highly active (IC_{50} of *ca.* 2-3 nM) against breast and ovarian cancer cell lines.

The HCT-116 colon carcinoma line used for Fenical's studies developed 'super' sensitivity on two occasions towards cytotoxins. Although standards are used in each run, the new cytotoxins can be more active towards these cells than others.¹²

Another possibility is that the natural product contained a highly active impurity resulting from the reliance of HPLC and NMR assays as an indication of

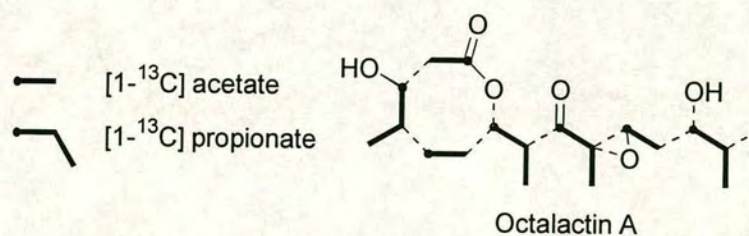
purity. However, this is unlikely and the inactivity is probably a result of different cell lines used.

It is interesting to note that one of the more simple of Buszek's intermediates **18** (Scheme 5) showed a partial blockage of tubulin polymerisation suggesting that it might be a novel microtubule de-stabilising agent.¹³ Studies in this area of synthesis are, therefore, still of interest to the organic chemist.



Scheme 5 Buszek's active intermediate

A polyketide origin to the octalactins has also been proposed. Although no labelling/incorporation studies have been carried out to confirm this theory, a potential [1-¹³C] labelling pattern is depicted in Scheme 6.



Scheme 6 Possible labelling pattern for octalactin A

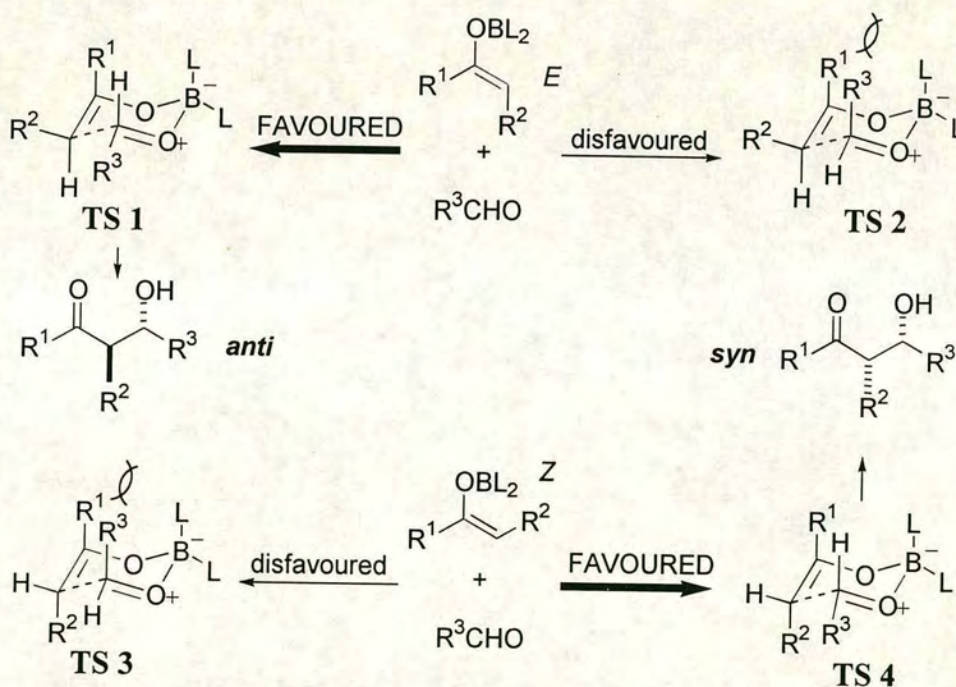
The increasing complexity of natural products with biological activity has prompted vast interest in methodology geared towards their synthesis, particularly that of polyketides.¹⁴

A selection of these methodologies will be discussed in the following sections of this chapter together with the potential of application to this class of natural products.

1.3 ASYMMETRIC BORON ALDOL REACTION

1.3.1 Relative Stereocontrol

The relative stereochemistry of the kinetically controlled boron aldol reaction has been shown to be related directly to the *E:Z* geometry of the enol borinate intermediate formed in the presence of a tertiary amine base. The diastereoselectivity of the reaction can be rationalised by considering the reaction to go *via* a preferred transition state structure (TS 1 or TS 4), according to the Zimmerman-Traxler model.¹⁵ In the favoured transition states, TS 1 and TS 4, the aldehyde chain (R^3) adopts a more favoured pseudo equatorial position, avoiding any diaxial interactions which occur in the transition states TS 2 and TS 3 (Scheme 7).

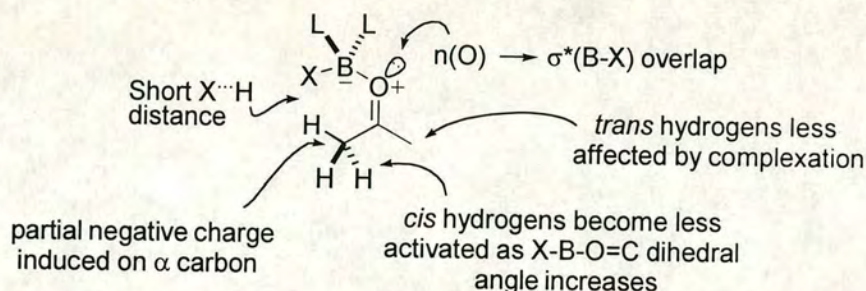


Scheme 7 Relative stereocontrol in the boron aldol reaction

The steric requirements of the L groups in the boron reagent as well as the R^2 group on the enolate have also been shown to have a substantial effect on the enolate geometry.¹⁶

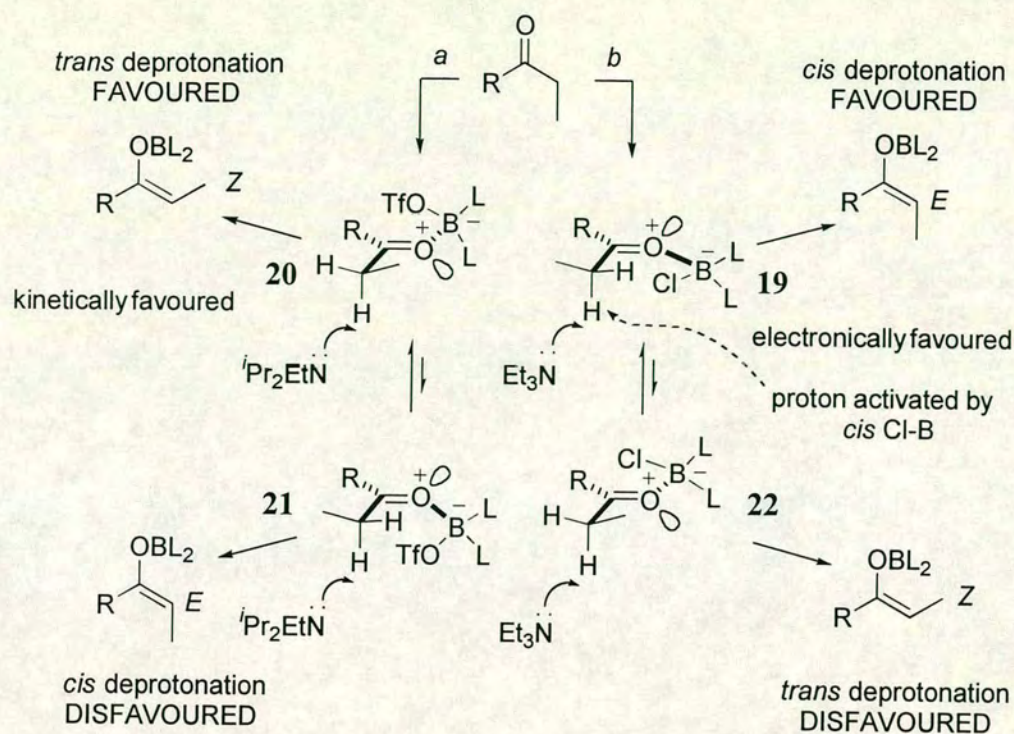
L_2BX reagents with a variety of ligands and leaving groups have been used to generate either the *E* or *Z* enol borinates for a number of different substrates including ketones¹⁷ and thioesters.¹⁸ Brown has shown that L_2BX reagents with better leaving groups (mesylate or triflate) favour the formation of *Z* enol borinates, whereas those with poorer leaving groups (chloride or bromide) favour *E* enol borinate formation.¹⁶

There are two possible hypotheses which have been proposed to explain the stereochemical selectivity of enolate formation. Recent molecular orbital calculations by Goodman and Paterson on $R^1R^2CO \cdot BH_2X$ complexes ($X=F, Cl$) (used as a model for $R^1R^2CO \cdot BL_2X$ complexes) have shown that there is a generalised anomeric effect between the uncomplexed lone pair of the carbonyl and the B-X antibonding orbital (σ^*), causing the B-X bond to eclipse the C=O bond (**Scheme 8**).^{19,20}



Scheme 8 $R^1R^2CO \cdot BL_2X$ complex model

The halogen is thus directed towards one of the protons on the *cis* alkyl group, inducing a partial negative charge on this α -carbon (thereby activating the *cis* side towards deprotonation by an unhindered base such as Et_3N via **19**).

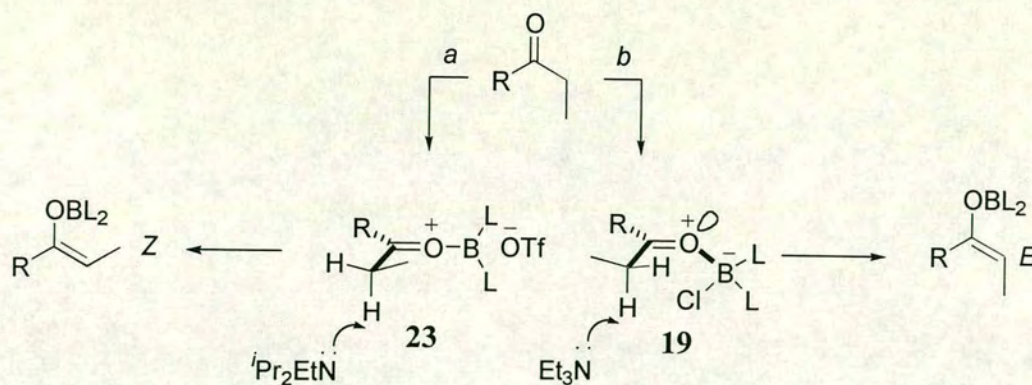


(a) L_2BOTf , iPr_2NEt ; (b) L_2BCl , Et_3N .

Scheme 9 Deprotonation selectivity (Goodman/Paterson)

As the X-B-O=C dihedral angle increases (e.g. as induced by sterically bulky triflate ligands) the electronic influence on the *cis* alkyl group decreases and *trans* deprotonation is favoured by a bulky base such as iPr_2NEt (via **20**) (**Scheme 9**).

A second explanation was postulated by Corey who proposed that the superior leaving group ability of the triflate allows the formation of a linear intermediate **23**.²¹



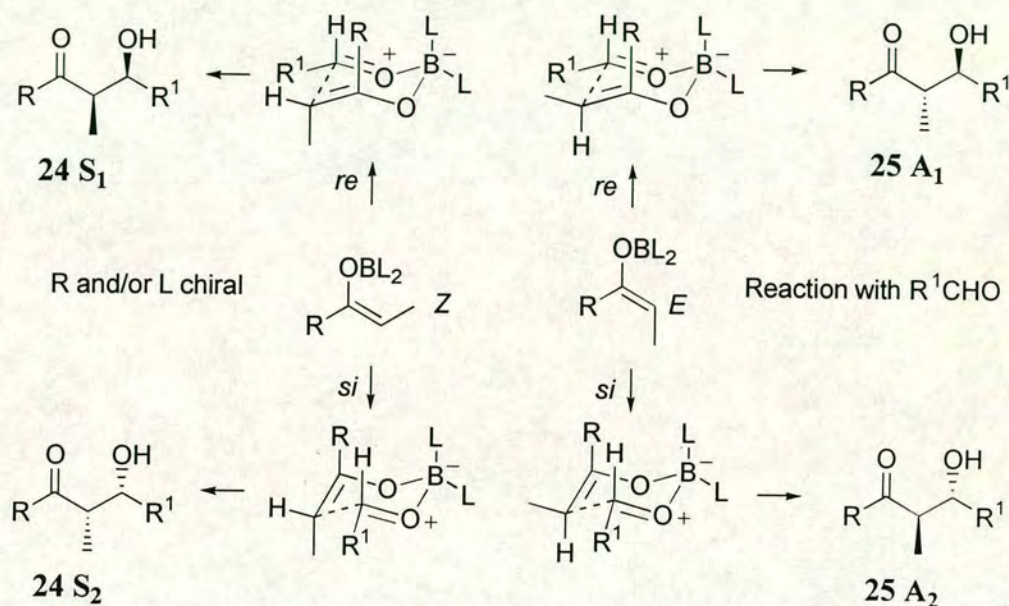
(a) L₂BOTf, ⁱPr₂NEt; (b) L₂BCl, Et₃N.

Scheme 10 Deprotonation selectivity (Corey)

The methyl group is then able to eclipse the C=O-BL₂ bond and thus deprotonation to give the Z-enolate (E1-like mechanism) *via* **23** is favoured. With a poorer leaving group (Cl), a bent B-Cl complex ensues, and then steric hinderance only allows deprotonation to give the E-enolate (E2-like mechanism) *via* **19** (Scheme 10).

1.3.2 Absolute (*anti*) Stereocontrol

Absolute stereocontrol in the boron aldol reaction demands that the enolate should show a high level of π -facial selectivity. One of the π -faces of the enolate must, therefore, be selective for either the *si* or *re* faces of the aldehyde. The *E* enolate giving the *anti* isomers and the *Z* enolate the *syn* isomers.

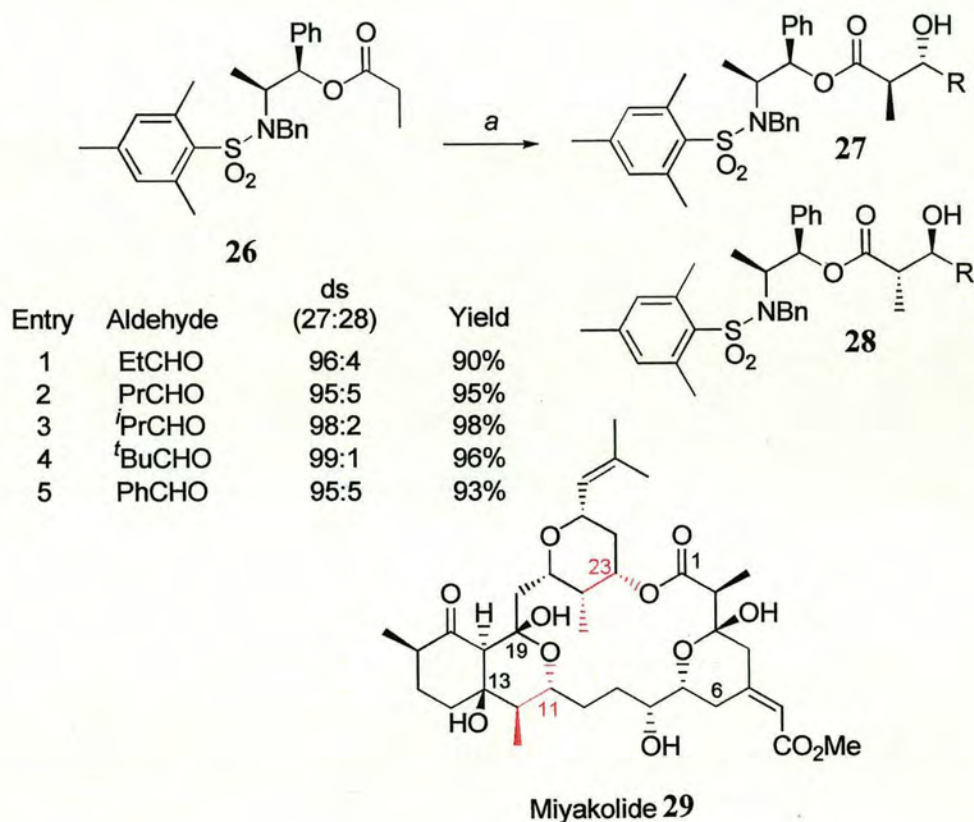


Scheme 11 *Enantiofacial selectivity*

The *syn*- and *anti*-3-hydroxy-2-methyl carbonyl units **24** and **25** are frequently found in natural products of polypropionate origin.¹⁴ Whilst the construction of the *syn* unit **24** can be attained efficiently through an asymmetric aldol reaction, the search for synthetic methods for efficient generation of the *anti* unit **25** remains of interest to the organic chemist. Several methods now exist for a stereoselective *anti* aldol reaction.

- the use of chiral ligands on boron,²² titanium²³ or tin(II) enolates²⁴
- the asymmetric version of the Mukaiyama (Lewis acid catalysed) aldol²⁵
- the use of a metal enolate derived from a chiral carbonyl compound²⁶

In most of these cases the *anti* aldol product can be generated with high enantioselectivity. However, there appear to be problems associated with some of these methods in terms of the availability of reagents, the generality of the reactions or the relatively harsh conditions required for conducting the reactions. Recently Masamune appears to have overcome most of these hurdles through the design of the carboxylic ester **26**.²⁷



(a) i. ^tPr₂EtN, (C₆H₅)₂BOTf, CH₂Cl₂, -78 °C, 2 h; ii. RCHO, -78 °C, 1 h, then 0 °C for 1 h.

Scheme 12 Masamune's auxiliary

This auxiliary gives excellent yields and selectivities in the *anti*-selective boron mediated aldol reaction with a variety of aldehydes to give the *anti* diastereomers **27** and **28** with no formation of the *syn* diastereomers (Scheme 12).

Masamune has demonstrated its utility in the synthesis of the C(6)-C(13) and C(19)-C(28) fragments of Miyakolide **29**.²⁸ The ester **26** and its enantiomer (both readily available from the corresponding enantiomers of norephedrine) were used for the construction of the C(11)-C(12) and C(22)-C(23) bonds respectively (**Scheme 12**).

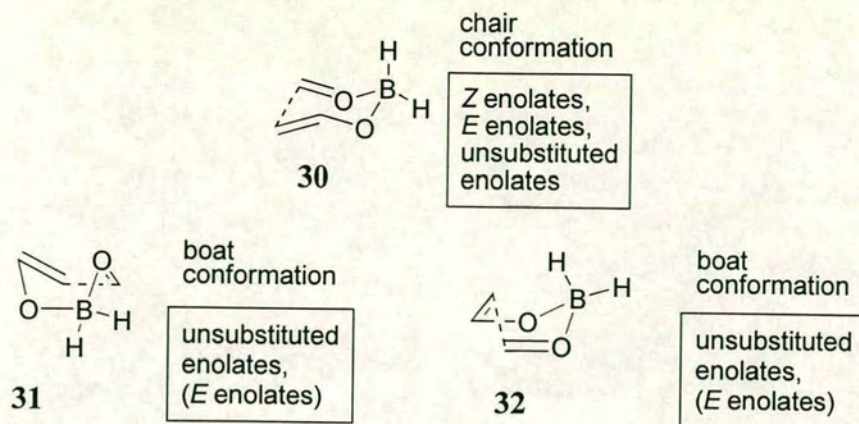
1.4 ACETATE ALDOL COUPLING

The well-established Zimmerman-Traxler transition state model has been proposed to explain the products of various aldol addition processes. This transition state accounts very well for the general observation that the aldol reactions from α -substituted boron enolates exhibit a high degree of stereoselection as discussed in the previous section. However, on consideration of the acetate (α -unsubstituted) enolate there is a large reduction in the levels of asymmetric induction.

1.4.1 Selectivity in the Boron-mediated Acetate Aldol

High selectivity for the unsubstituted (acetate) aldol reaction is more difficult to attain due to the fact that unsubstituted boron enolates have access to a number of transition states when compared to their propionate counterparts (discussed in **Section 1.3.1**).

The chair **30** and the two boat conformations **31** and **32** as depicted in **Scheme 13**, have been shown through *ab initio* calculations by Goodman²⁹ to be the core conformations for the transition state.



Scheme 13 Transition state structures determined by *ab initio* calculations

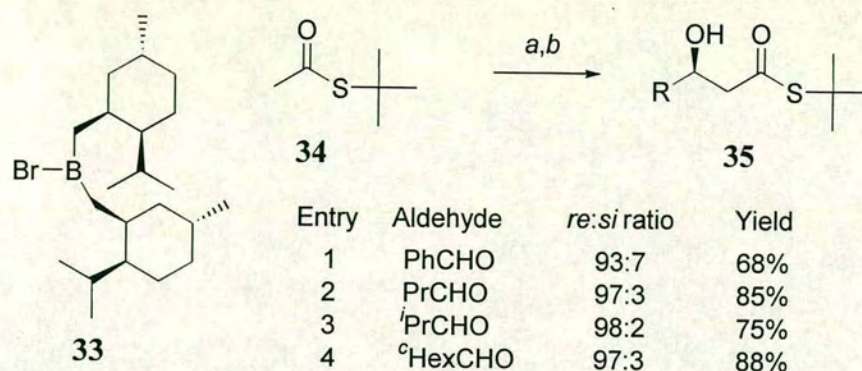
The competition between the transition state structures which have similar energies makes the stereochemical nature of the reaction much more difficult to control.

1.4.2 Recent advances in the Acetate Aldol reaction

Impressive progress in the search of reliable aldol methodology for the generation of an α -unsubstituted β -hydroxy carbonyl unit has been made recently and some of the various methods available will be discussed briefly in the following section.

Chiral ligand control

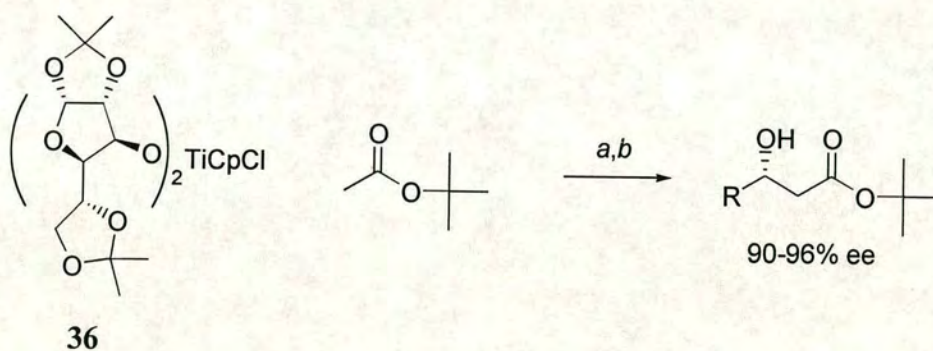
The computer-designed reagent **33** introduced by Gennari¹⁸ has been used for the enolisation of thioacetates **34** to give the corresponding β -hydroxythioesters **35** with high enantioselectivity as depicted in **Scheme 14**.



(a) **33**, Et₃N; (b) RCHO.

Scheme 14 *Enantioselective synthesis of unsubstituted β -hydroxy thioesters*

Duthaler has used the chiral titanium reagent **36** to transmetallate acetate lithium enolates giving high levels of enantioselective induction in their reaction with aldehydes (**Scheme 15**).²³

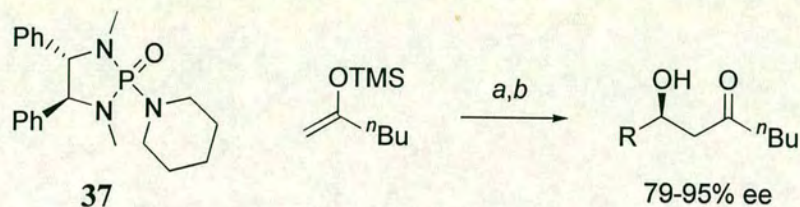


(a) LDA, **36**; (b) RCHO.

Scheme 15 *Enantioselective synthesis of unsubstituted β -hydroxy esters*

Chiral catalysts

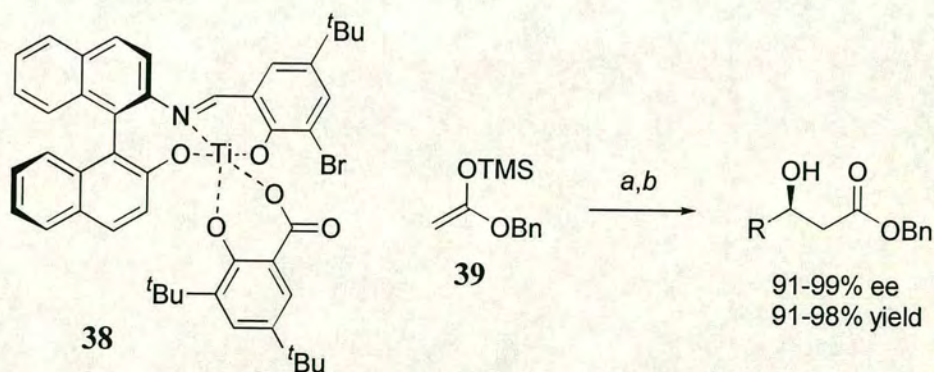
Denmark has recently developed a stilbene diamine-derived phosphoramidate **37** catalyst for the Lewis base-catalysed aldol reaction of methyl ketone silyl enol ethers (Scheme 16).³⁰



(a) SiCl_4 , 1 mol% $\text{Hg}(\text{OAc})_2$; (b) 5 mol% **37**, RCHO.

Scheme 16 *Lewis base-catalysed aldol reaction*

However, possibly the best selectivities in this class of reaction have come from Carreira who has recently developed a complex titanium-based catalyst **38** for the acetate aldol reaction of silyl ketene acetals.³¹



(a) 2 mol% **38**, RCHO; (b) 10% TFA.

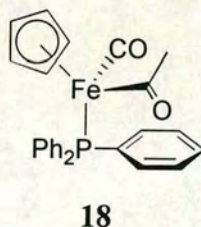
Scheme 17 *Titanium-based enantioselective acetate aldol reaction*

Reaction of the silyl ketene acetal **39** with aldehydes in the presence of 2 mol% of the catalyst gives excellent yields and enantioselectivities of the corresponding aldol adducts (**Scheme 17**).

Chiral Auxiliary control

A variety of auxiliary-based approaches have been utilised to obtain α -unsubstituted β -hydroxy carbonyl units stereoselectively. Modification of the Evans oxazolidinone with a hetero atom at the α position (*e.g.* Cl/Br³² or SMe³³) can give high selectivities in the aldol reaction. The hetero atom can then be removed at a later stage to give the ‘clean’ α -unsubstituted β -hydroxy carbonyl unit.

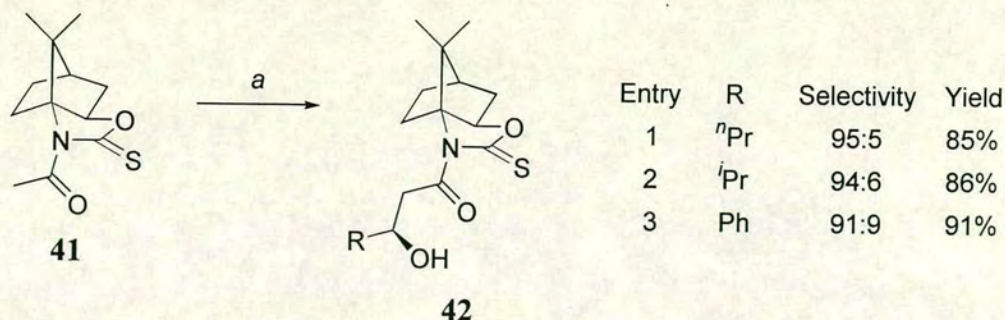
The best yields and selectivities in the acetate aldol reaction come from the ‘Rolls Royce’ of chiral auxiliaries **40** (**Scheme 17**) developed by Davies³⁴ in 1984. This auxiliary however, cannot be recycled and is expensive to prepare.



Scheme 18 *Davies' Fe-based acetate auxiliary*

Indeed, all of the above established approaches have their shortcomings, therefore, the search for a widely applicable process continues.

Recently Yan³⁵ has reported the synthesis and use of camphor derived auxiliary, **41** in its titanium mediated aldol reaction with a wide selection of aldehydes (**Scheme 19**).



(a) TiCl_4 , $^i\text{Pr}_2\text{EtN}$, CH_2Cl_2 , $-70\text{ }^\circ\text{C}$, 2h.

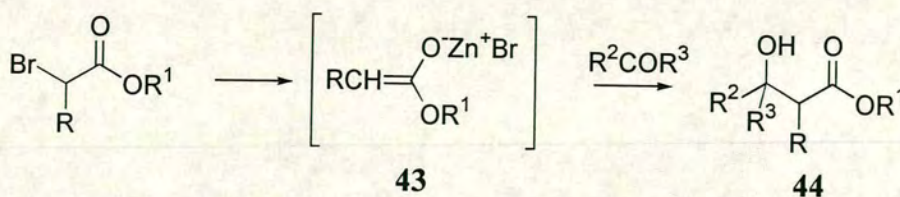
Scheme 19 Titanium mediated acetate aldol

This methodology offered consistently high levels of stereoinduction giving aldol adducts **42**. This, coupled with the relatively low cost of TiCl_4 compared to the other metal acids (*e.g.* Bu_2BOTf , $\text{Sn}(\text{OTf})_2$) and the possibility of auxiliary recovery make **41** quite an attractive choice for the acetate aldol reaction.

The success of this titanium enolate in the acetate aldol reaction has prompted the search for an improved camphene derived auxiliary, the synthesis of which will be discussed in **Chapter 4**.

1.5 REFORMATSKY REACTION

The Reformatsky reaction along with other aldol-like processes, may be regarded as a two step reaction with enolate **43** formation and then reaction with an aldehyde or ketone in the actual aldol reaction (**Scheme 20**) to give a β -hydroxy ester **44**.³⁶



Scheme 20 The Reformatsky reaction

The Reformatsky variation offers a number of advantages.

- the enolate can invariably be formed at a predetermined site
- essentially neutral reaction conditions required
- potential to conduct the reaction in the presence of several other functional groups
- the activated position may differ from those that are accessible through kinetic or thermodynamic base-induced enolisation

1.5.1 The Chromium-Mediated Reformatsky Reaction

The major disadvantage of the traditional procedure with zinc is low reactivity, low reproducibility, and the ability to access only thermodynamic products.

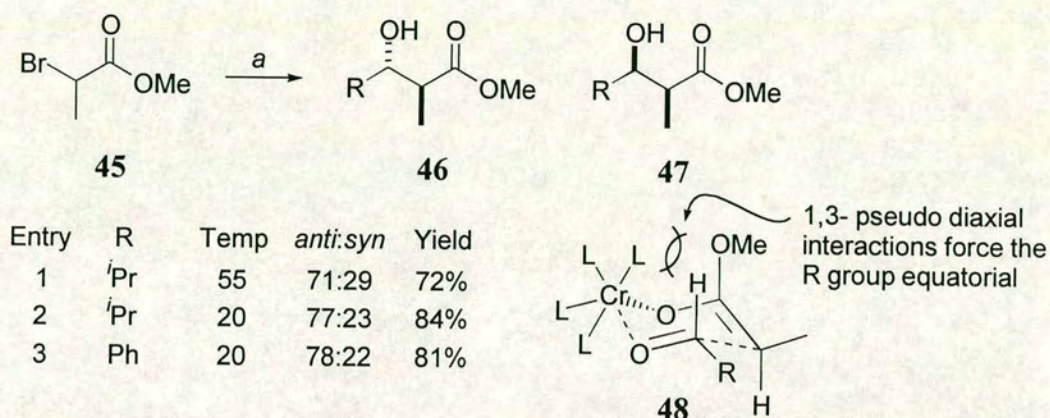
The low yield and selectivities in the reaction arise from the low reactivity of the zinc metal. The reaction as a result usually has to be carried out at high temperature causing undesirable side reactions. There has been a concerted effort in this area with the use of samarium,³⁷ low-valent germanium³⁸ and activated zinc³⁶ in attempts to improve on the stereoselectivity and yields for this reaction.

Wessjohann has recently described the use of an activated chromium species which offers excellent reproducibility, convenient handling without activation and excellent chemoselectivity with improved diastereoselectivity over the traditional zinc mediated reaction.³⁹

Reaction of the α -bromo ester **45** with either isobutyraldehyde or benzaldehyde in the presence of CrCl_2 and LiI ⁴⁰ gave good yields of the β -hydroxy esters **46** and **47** at ambient temperatures (**Scheme 21**). In contrast to the products

⁴⁰ Lithium iodide is added to the reaction as it results in clean reactions and higher yields. The effect of its addition includes general lewis acid and nucleophilic iodide catalysis. However, the main influence of lithium iodide in the reaction is thought to be through its ability to solubilise and modify the nature of the chromium dichloride. The active species, whilst still unknown, has been proposed by Wessjohann to be a $\text{Li}_2[\text{CrX}_4\text{L}_2]$ species or similar complex.³⁹

observed for the zinc mediated reaction, a preference for the *anti* diastereomer **46** was observed.



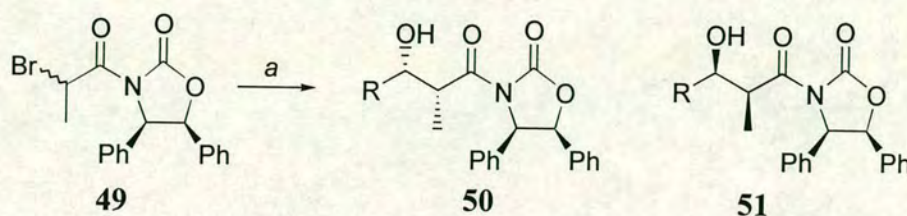
(a) CrCl_2 , LiI, RCHO, THF.

Scheme 21 Chromium mediated Reformatsky

A slight preference for the *E*-enolate, giving rise to the *anti* aldol adduct via Zimmerman-Traxler transition state **48** was used to explain the low levels of *anti* selectivity (Scheme 21).

1.5.2 Asymmetric Reformatsky Reaction

Recently there have been several successful methods developed for the asymmetric version of the Reformatsky reaction.^{36-38,40}



Entry	R	50:51	Yield
1	<i>n</i> Pr	99:1	86%
2	<i>i</i> Pr	99:1	79%
3	Ph	99:1	81%

(a) i. GeI_2 , K, THF; ii. **49**, RCHO, THF.

Scheme 22 Germanium mediated asymmetric Reformatsky

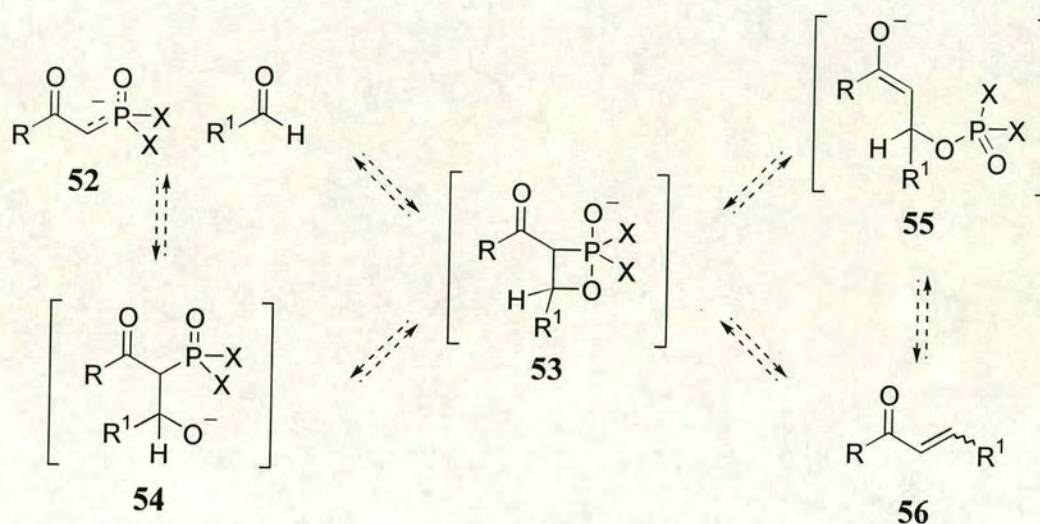
Hashimoto³⁸ has recently described the use of a low-valent germanium species for use in the Reformatsky reaction using an Evans-type auxiliary **49** to give high yields and excellent diastereoselectivity for the Evans *syn* diastereomer **50** (Scheme 22). (Only small amounts of the corresponding non-Evans *syn* **51** and *anti* diastereomers were observed.)

Hashimoto has proposed (on the basis of the absolute stereochemistry of the products produced in the reaction) that the diastereofacial selection occurs in the same manner as that in the aldol reaction of boron enolates (see Section 1.3). However, no attempts were made to assess the stereochemical nature of the germanium enolate.

Wessjohann has used a similar strategy in the use of an activated chromium species to generate the non-Evans *anti* aldol products, as will be discussed in more detail in Chapter 4.

1.6 THE HORNER-WADSWORTH-EMMONS REACTION

The Horner-Wadsworth-Emmons (HWE) reaction is a versatile method for the formation of α,β -unsaturated compounds from a β -ketophosphonate **52** and an aldehyde to give the α,β -unsaturated ketone **56** (Scheme 23). The mechanism is believed to go *via* either an oxaphosphetane⁴¹ **53** or either diastereomer of the oxyanion intermediate⁴² **54**. The involvement of a ring cleaved enolate **55** has also been postulated (Scheme 23).⁴³

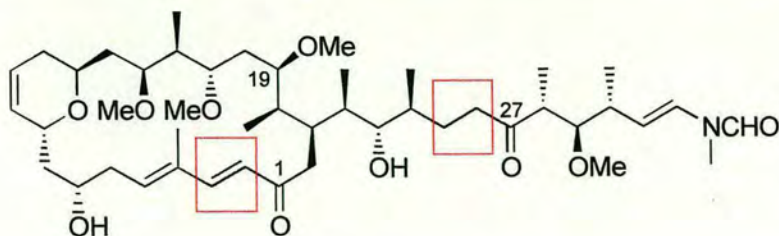


Scheme 23 The HWE reaction and possible mechanistic pathways

There have been numerous examples of the HWE coupling of aldehydes with β -ketophosphonates reported in the literature, including modifications to allow the use of milder conditions⁴⁴ (*i.e.* where the aldehyde is base sensitive/enolisable) or to promote the *E:Z* selectivity.⁴⁵

1.6.1 Barium-mediated HWE reaction

In their studies towards the cytotoxic macrolide scytophycin C **57**, Paterson *et al.*⁴⁶ chose to construct the C_2-C_3 and $C_{25}-C_{26}$ bonds *via* the HWE reaction (Scheme 24).



Scytophycin C 57

Scheme 24 *Scytophycin C*

Paterson found that barium hydroxide was most effective at promoting the reaction, where other bases had failed or had given poor *E:Z* selectivity. It has been suggested by Sinisterra⁴⁷ that the microcrystalline structure is crucial to the activity of barium hydroxide and that C-200 barium hydroxide^o is the most active form. Paterson also found that by heating commercial $\text{Ba}(\text{OH})_2 \cdot 8\text{H}_2\text{O}$ at 100-140 °C for 2 h gave good results.

The *E* alkenes were obtained exclusively in both C=C bond formation reactions and the base caused no enolisation of the base sensitive aldehydes. This method, thereby, offers a mild and effective method for the coupling of a β -ketophosphonate with base sensitive aldehydes giving α,β -unsaturated compounds stereoselectively in good yields.

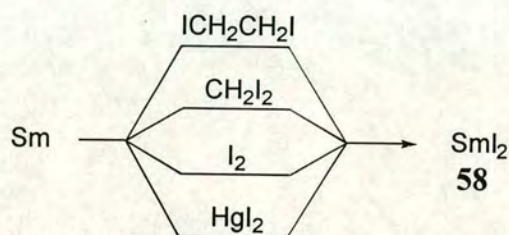
Applications of this methodology to the synthesis of tri-substituted alkenes will be described in **Chapter 2** and **Chapter 4**.

^o C-200 barium hydroxide has the empirical formula $\text{Ba}(\text{OH})_2 \cdot 0.8\text{H}_2\text{O}$ and is produced by heating $\text{Ba}(\text{OH})_2 \cdot 8\text{H}_2\text{O}$ at 200 °C for 3 hours.⁴⁷

1.7 SAMARIUM DIODIDE

Whilst the existence of samarium (II) diiodide **58** has been known for over 60 years,⁴⁸ it was not until 1980 that Kagan introduced it as a reagent for organic synthesis.⁴⁹ Since then it has been increasingly used for a variety of useful transformations.^{50,51}

Samarium (II) diiodide **58** can be prepared as a solution in THF from samarium metal by a number of different methods (**Scheme 25**).⁵²⁻⁵⁴



Scheme 25 Samarium diiodide formation

The reaction gives SmI_3 which is then reduced by samarium metal to give SmI_2 . The resulting deep blue solution can be stored in the absence of oxygen and in an anhydrous environment for a number of hours when stabilised with samarium metal. Although solutions of SmI_2 are commercially available, for synthetic purposes SmI_2 is generally prepared and used *in situ*.

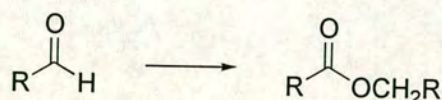
The reduction potential of $\text{Sm}^{+2}/\text{Sm}^{+3}$ measured in water is -1.55 V ,⁵⁵ making it a powerful reducing agent. However, the reduction potential of SmI_2 can vary widely dependant on the solvent and the addition of various additives, thereby affecting its ability to promote the reduction of different organic substrates.^{51,56}

SmI_2 initiates a number of selective coupling reactions and functional group conversions with halogen- and oxygen-containing substrates as well as many other reductions and couplings of miscellaneous functional groups. These transformations can be either radical or carbanionic in nature.⁵⁷

As a result, and as a testimony to its increasing importance, a number a detailed review articles are available which discuss in detail the use of SmI_2 as a reducing agent and as a reductive coupling reagent in organic synthesis.^{50,51,57}

1.7.1 The Tishchenko reaction

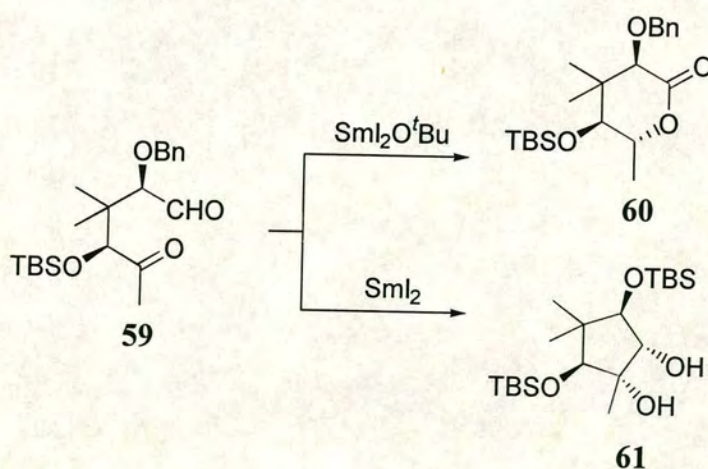
The Tishchenko reaction is defined as the coupling of 2 moles of aldehyde to give an ester (Scheme 26).



Scheme 26 *The Tishchenko reaction*

Kagan has shown that it is possible to conduct a Tishchenko-type coupling in the presence of an active Sm(III) catalyst formed from SmI_2 .⁵⁸

Uenishi⁵⁹ demonstrated the use of a Sm(III) species (again formed from SmI_2) to promote an intramolecular coupling akin to the Tishchenko reaction.



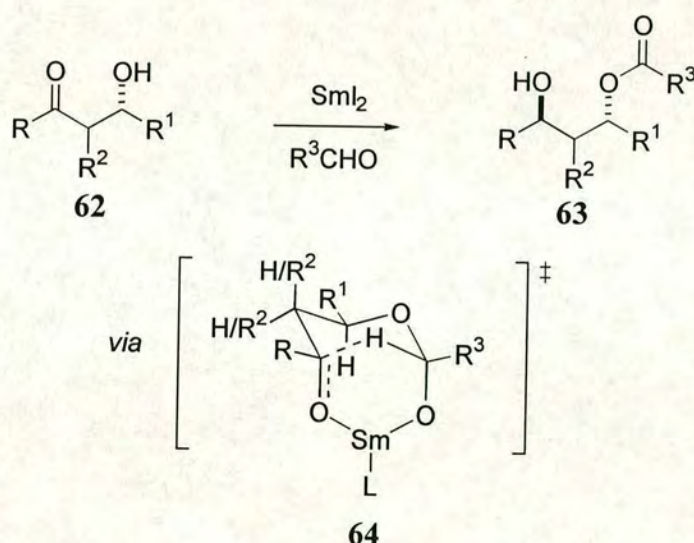
Scheme 27 *Intramolecular Tishchenko and pinacol couplings*

Reaction of keto-aldehyde **59** with $\text{SmI}_2\text{O}^t\text{Bu}$ gave the lactone **60** stereoselectively in good yield. Interestingly, reaction with SmI_2 alone gave the pinacol adduct **61** also in a stereoselective manner (**Scheme 27**). Reactions with other similar keto-aldehydes also gave the corresponding lactone and pinacol products.

Tishchenko cyclisation reactions with aluminium, lanthanum and zirconium based catalysts have also been reported.⁶⁰⁻⁶²

1.7.2 The Evans-Tishchenko reaction

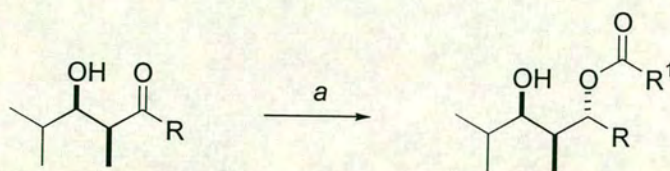
The reaction, as first demonstrated by Evans in 1991, is the coupling of an aldehyde with a β -hydroxy ketone **62** with concomitant stereoselective reduction of the ketone functionality giving the *anti* diol monoester **63** (**Scheme 28**).⁶³



Scheme 28 Evans-Tishchenko reaction

A possible mechanism has been suggested involving co-ordination of the aldehyde and the hydroxy ketone, hemiacetal formation and an intramolecular hydride transfer *via* a transition state similar to **64** (**Scheme 28**). Evans' syntheses proceeded smoothly with freshly prepared SmI_2 (30 mol%) in THF at $-10\text{ }^\circ\text{C}$ to give

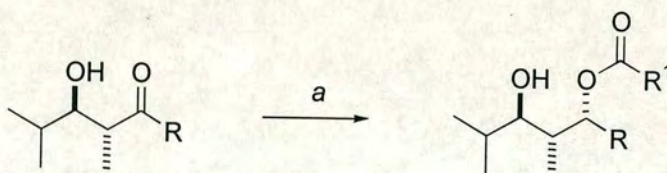
the diol monoesters in yields of 70-99% and *anti:syn* ratios of >99:1 in every case (Tables 1 and 2).



(a) 30 mol% SmI_2 , R^1CHO THF, -10°C .

Entry	R	R_1	Yield (%)	<i>anti:syn</i>
1	Et	Me_2CH	95	>99:1
2	Me_2CH	Me	85	>99:1

Table 1



(a) 30 mol% SmI_2 , R^1CHO THF, -10°C .

Entry	R	R_1	Yield (%)	<i>anti:syn</i>
1	Et	Me	86	>99:1
2	Me_2CH	Ph	95	>99:1

Table 2

Also noted was that the reduction of both *syn* and *anti* α -methyl- β -hydroxy ketones follow the same stereochemical course with a similar degree of asymmetric induction (Tables 1 and 2).

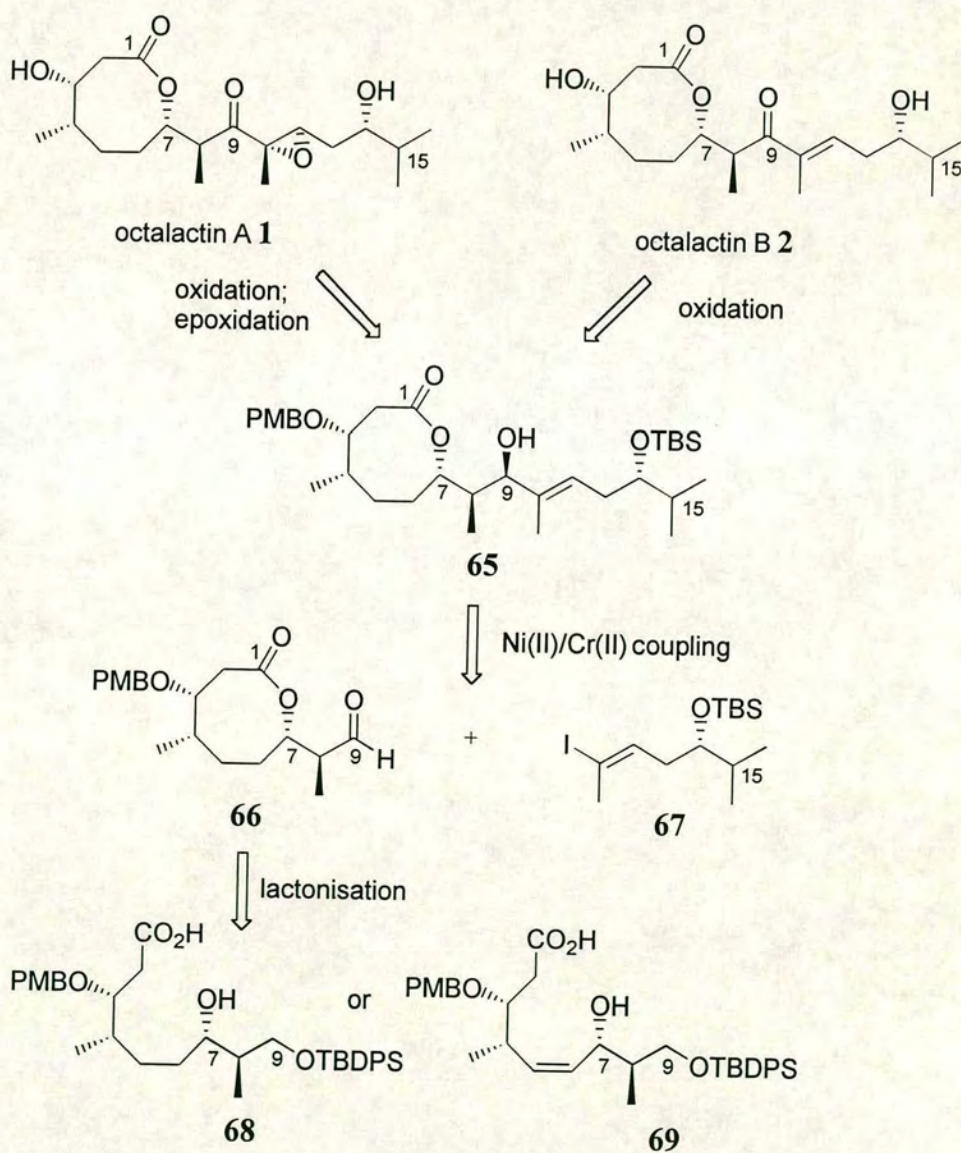
Since the introduction of the reaction by Evans there have been a number of applications of the reaction to natural product synthesis.^{64,65}

An intramolecular version of the Evans-Tishchenko reaction has been identified as a key step in a strategy (see **Section 2.1**) towards the synthesis of octalactin A **1**, offering a novel method for the synthesis of this cytotoxic eight-membered ring lactone natural product.

CHAPTER 2

MODEL STUDIES

As discussed in the previous chapter, octalactin A **1** and octalactin B **2** (Scheme 29) were isolated in 1991 from an unidentified marine-derived actinomycete found on the surface of a gorgonian octocoral (*Pacifigorgia* sp.) in the Gulf of California, Mexico.⁷

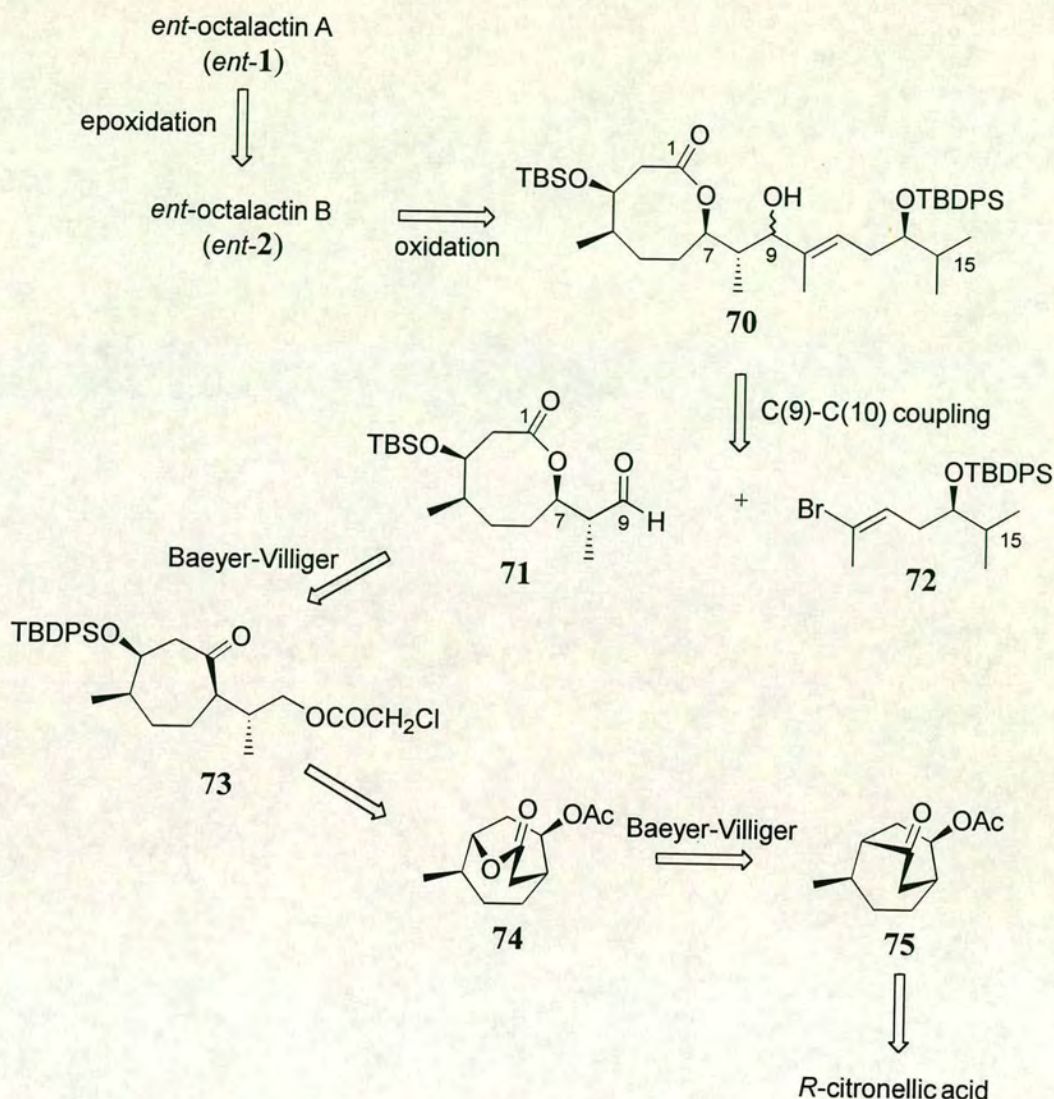


Scheme 29 Buszek's synthesis of the octalactins

Due to their interesting structure, including a fully saturated eight-membered lactone ring, and the significant *in vitro* cytotoxicity reported, there have been a number of synthetic approaches to the octalactins.⁶⁶⁻⁷² The syntheses by Buszek⁶⁸ and Clardy⁷² (synthesis of *ent*-octalactin A and *ent*-octalactin B) were the first and served to confirm the absolute stereochemistry of these two marine metabolites.

Buszek's synthesis of the octalactins relies on a common intermediate **65** synthesised from a Ni(II)/Cr(II)-mediated coupling of the C(1)-C(9) fragment **66** and the C(10)-C(15) fragment **67**. The stereochemistry at C(9) in **65** allowed for the hydroxyl directed introduction of the epoxide in the required manner. The key step in this synthesis was envisaged to be the lactonisation of the unsaturated hydroxy acid **68** but the double bond proved to be impossible to reduce after cyclisation. Therefore, the actual synthesis favoured the unprecedented lactonisation of the saturated hydroxy acid **69** (Scheme 29).

The absolute stereochemistry of the octalactins was not known when Williams and Clardy began their synthesis. After completing their total syntheses it became clear that they had arbitrarily synthesised the unnatural antipodes *ent*-**1** and *ent*-**2**. The latter stages of this synthesis were very similar to that of Buszek's with the C(1)-C(9) fragment **71** being coupled with the C(10)-C(15) fragment **72** giving intermediate **70**. The route to **71** however, differed entirely from the Buszek approach. The eight-membered lactone ring was synthesised by a Baeyer-Villiger oxidation of the ketone **73** and the precursor **74** to this ketone was also obtained through a Baeyer-Villiger oxidation of the key diketone intermediate **75**, synthesised from *R*-citronellic acid in 8 steps (Scheme 30).

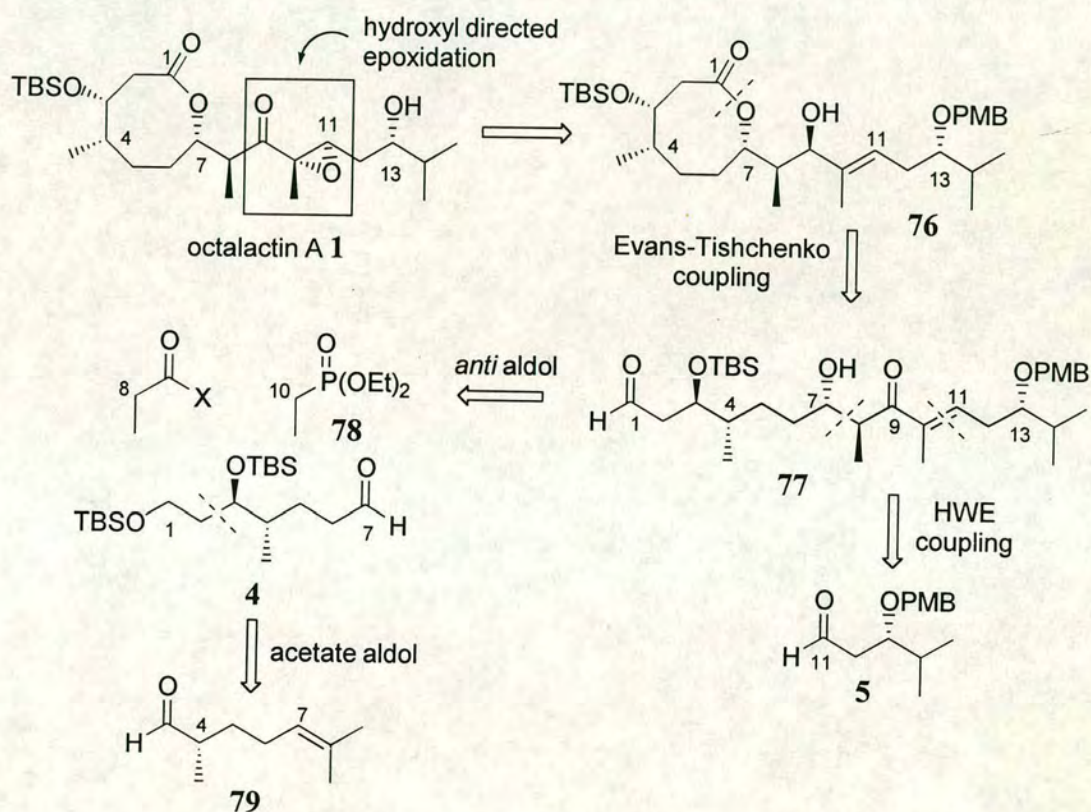


Scheme 30 Clardy's synthesis of the octalactins

2.1 RETROSYNTHETIC ANALYSIS OF THE OCTALACTINS

A retrosynthetic analysis for octalactin A is shown in **Scheme 31**. The strategy relies on a novel cyclisation step which makes use of recent samarium based methodology used in the Evans-Tishchenko reaction of β -hydroxy ketones, producing *anti* 1,3-diol monoesters with excellent stereoselectivity.⁶³ The reaction would cause concomitant reduction of the ketone functionality at C(9) to give **76**. With the correct stereochemistry in place at C(9), it is possible to direct the epoxidation at C(10)-C(11) in the required manner as previously demonstrated.^{68,72} The C(10)-C(11) double bond may be constructed through a Horner-Wadsworth

Emmons (HWE) reaction between aldehyde **5** and a suitable β -keto phosphonate. The stereocentre at C(13) of aldehyde **5** would be created utilising the thiazolidinethione acetate auxiliary **149** (Section 4.1) developed by Nagao.⁷³ An *anti* aldol coupling reveals the route through which the C(7)-C(8) bond and stereochemistry would be constructed (it was envisaged that the remote stereocentres in aldehyde **4** would not exert any control in the aldol reaction). Displacement of a suitable leaving group with the anion of phosphonate **78** would then set up a β -keto phosphonate for introduction of aldehyde **5**.



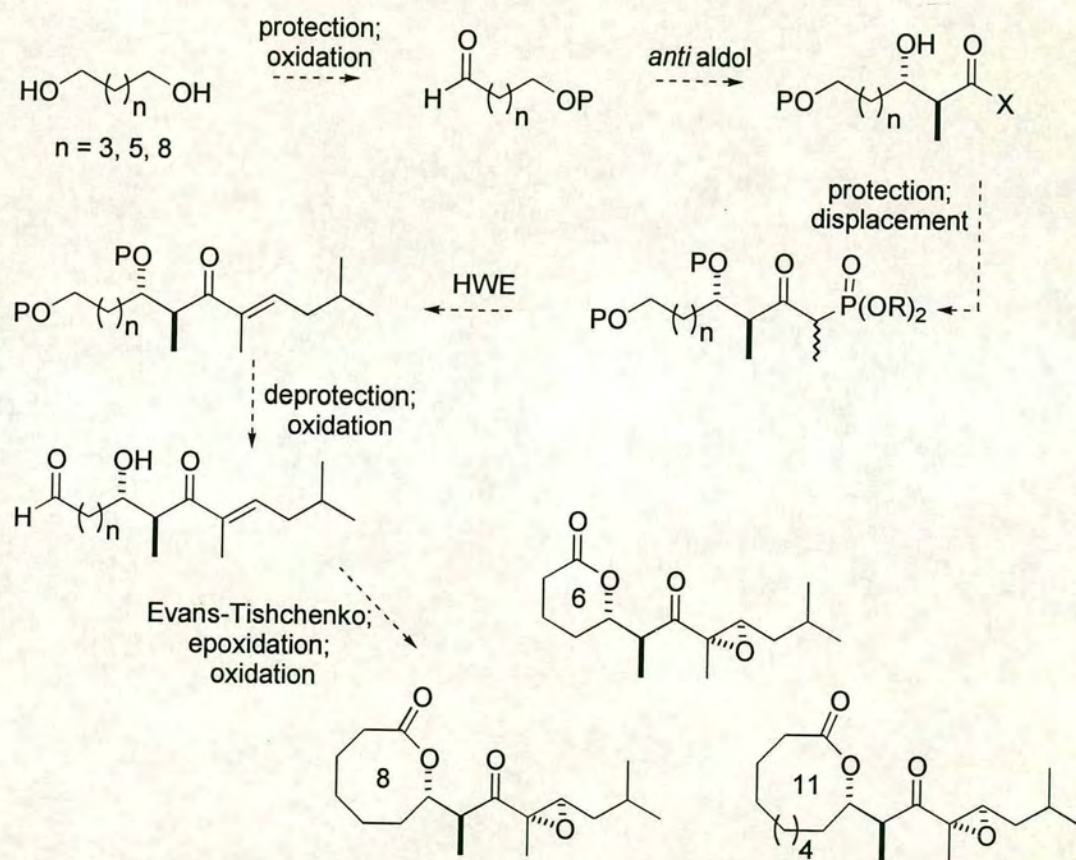
Scheme 31 Retrosynthetic analysis for octalactin A **1**

The HWE adduct could then be modified by a series of functional group interconversions to give the cyclisation precursor **77**. It was conceived that the C(4) stereocentre in aldehyde **4** could arise from an asymmetric epoxidation of the cheap and readily available geraniol followed by subsequent conversion to the known

aldehyde **79**. A further acetate type aldol coupling would then set up the stereocentre at C(3).

The strategy proposed, in contrast to previous syntheses, allows for the stereoselective generation of the alcohol functionality at C(9) in **76**.

In order to investigate the cyclisation reaction, as well as the feasibility of the other major steps in the synthesis, it was decided to conduct a series of model studies using simple, unfunctionalised systems before applying them to a total synthesis. Starting from the readily available 1,*n*-diols ($n = 3, 5$ or 8), it was envisaged that model compounds containing unfunctionalised lactone rings, could be synthesised using the key steps required for the total synthesis as discussed above (**Scheme 32**).

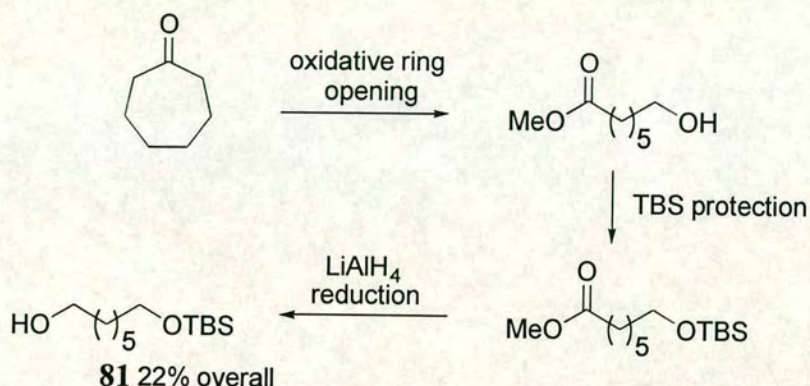


Scheme 32 Proposed synthesis of model compounds

2.2 SYNTHESIS OF UNFUNCTIONALISED ALDEHYDES

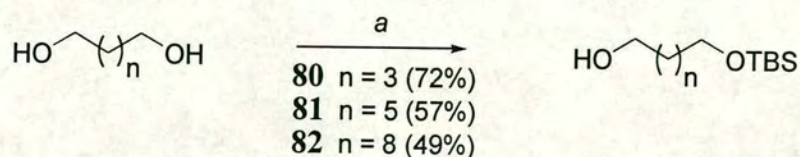
2.2.1 Monoprotection of symmetric diols

A previous synthetic approach to the monosilylated diol **81** used in this laboratory involved 3 steps: 1) oxidative ring opening of cycloheptanone, 2) protection of the alcohol as its TBS ether and 3) reduction of the ester gave an overall yield of 22%.



Scheme 33 Previous synthesis of monoprotected diol **81**

While there are a number of methods for the selective protection of unsymmetrical diols, the selective protection of symmetrical diols can still be a problem.⁷⁴ Statistically, if stoichiometric amounts of reagents are used then the maximum yield for monoprotection is only 50%.⁷⁵



(a) i. NaH, THF, rt, 40 min; ii. TBSCl, rt, 25 min.

Scheme 34 Monosilylation of 1,*n*-diols

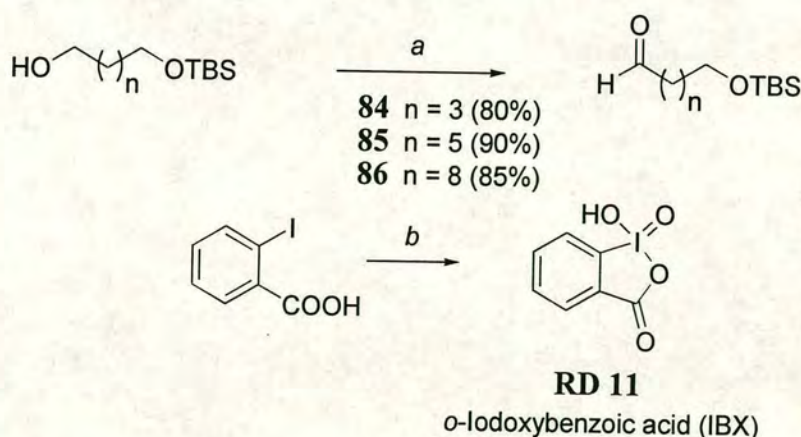
This has been overcome previously by using a large excess of diol or by continuous solvent extraction to remove the desired product.⁷⁶ McDougal⁷⁴ has since developed a method for the monosilylation of symmetric diols which would give an immediate route to **81** as well as monosilylated diols **80** and **82** (Scheme 34).

Treatment of the diol with one equivalent of sodium hydride causes the formation of a white precipitate, which is believed to be an aggregate of the monosodium salt. This precipitation thus removes any basic species from the reaction. Addition of the silylating agent causes the small amount of dissolved sodium salt to be silylated. As more of the salt becomes solvated, the rate of silylation is faster than the rate of deprotonation of the monosilylated diol thus resulting in a better than statistical yield of monosilylated product (Scheme 34).

McDougal's methodology was applied and resulted in the monosilylated diols **80-82** in moderate to good yield (49-72%).

2.2.2 Oxidation of Protected Diols

The mild oxidising agent *o*-iodoxybenzoic acid (IBX) **83** (Scheme 35) was employed for the oxidation of the monosilylated diols. Due to its limited solubility in common organic solvents, IBX has been used only as a precursor to the widely exploited Dess-Martin periodinane.⁷⁷



(a) IBX, THF/DMSO, rt, 1.5h; (b) KBrO₃, H₂SO₄ (0.7 M), 70 °C, 3.5 h.

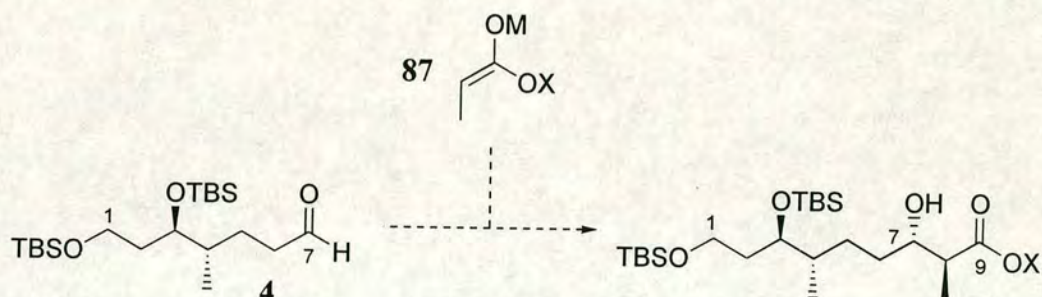
Scheme 35 Oxidation of monosilylated diols

However, Frigerio⁷⁸ discovered in 1994 that, contrary to literature data, IBX was indeed readily soluble in DMSO and for those substrates insoluble in DMSO, THF could be employed as a co-solvent. More recently Corey⁷⁹ has also used IBX for the mild oxidation of 1,4-diols to their corresponding lactols without further oxidation to the lactones. IBX is now an important addition to the repertoire of oxidising agents available to the synthetic chemist and has found application in a number of total syntheses.⁸⁰ IBX was synthesised by the method of Dess and Martin⁷⁷ from *o*-iodo benzoic acid and the methodology used by Frigerio⁷⁸ applied to alcohols **80-82**, giving excellent yields (80-90%) and no apparent over-oxidation to the acids. Stirring 1.5-2.0 equivalents of IBX in DMSO in an open flask produced a clear solution of ~0.3-0.5 M concentration in 20 to 30 minutes. One equivalent of the monosilylated diol was added in a solution of THF and oxidation was usually complete within 2 h, giving the aldehydes **84-86** (Scheme 35).

2.3 ANTI ALDOL APPROACH TO THE C₇-C₈ BOND CONNECTION

Until relatively recently the reactions of *E*-enolates had not been developed to the same extent as their corresponding *Z* isomers. Paterson²⁶ has shown how lactate derived chiral ketones can be used effectively, giving excellent yields and diastereoselectivities of the desired *anti* aldol adducts, which may then be further manipulated.

However, there are a limited number of protocols available for the reaction of aldehyde **4** with an *E*-enolate of a propionate **87** to give an *anti* aldol adduct stereoselectively (Scheme 36). Such a reaction is required for the C₇-C₈ bond connection in the synthesis of octalactin A as shown in the retrosynthetic analysis at the start of the chapter (Scheme 31).



Scheme 36 Proposed Aldol coupling for the C(7)-C(8) bond formation

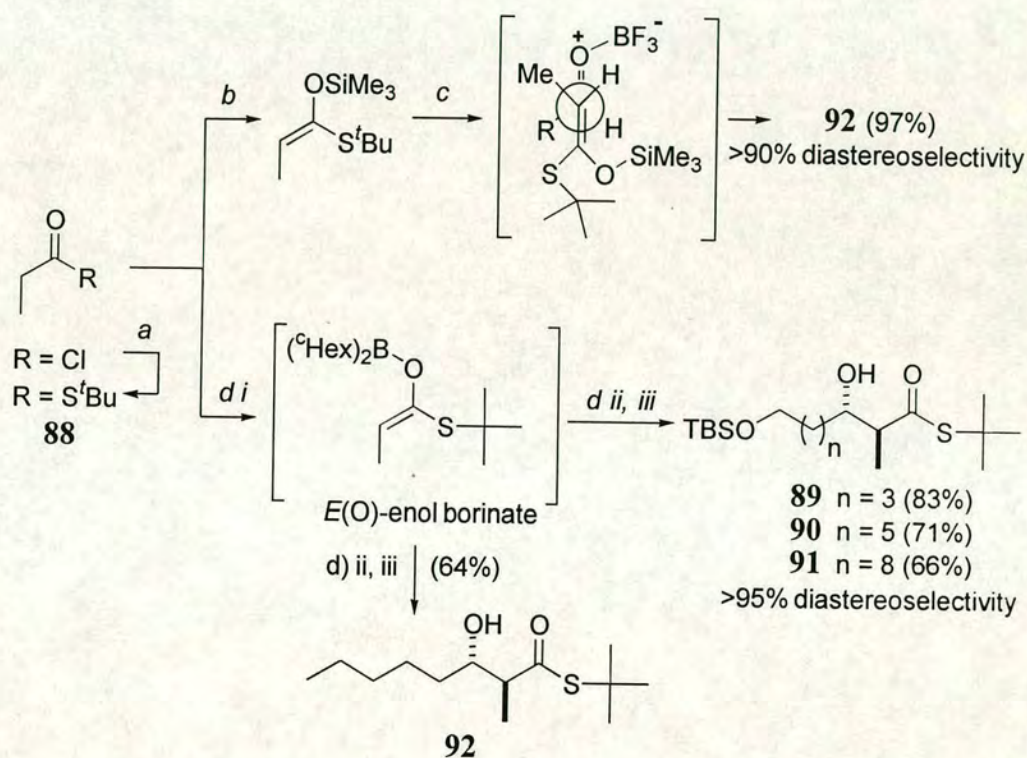
2.3.1 Thioester Methodology

Due to the enhanced α -hydrogen acidity in thioesters, processes such as enolate formation and Claisen condensation are highly favoured.⁸¹ These compounds are more electronically similar to ketones than to esters owing to the relative weakness of overlap of the C(2p) and S(3p) orbitals. Therefore, thioesters exhibit similar selectivity to that shown by ketone enolates.

The preparation of *E*-enol borinates from thioesters is well documented. Studies by Masamune⁸² have shown that the enolisation of thioesters with Hunig's base and a chiral boron triflate, followed by addition of an aldehyde give good yields of the corresponding aldol adducts. The reaction can be made either *syn* or *anti* selective by varying the nature of the thioester. For example, a bulky group on the

thioester leads to a large selectivity for the *E*-enol borinate and consequently a greater amount of the *anti* diastereomer produced.

It is also possible to exert high levels of enantioselectivity by the choice of the appropriate ligand on boron as alluded to above. As a result thioesters have been used extensively for the stereoselective synthesis of a number of polyketide natural products containing *anti* stereochemistry.⁸¹ It was, therefore, decided to employ thioester **88** as an achiral propionate equivalent for the C(7)-C(8) bond connection, and to couple simple aldehydes with the thioester in an *anti* aldol fashion.



(a) $^t\text{BuSH}$, Et_3N , Et_2O , rt, 51 h (64%); (b) i. LDA , THF , -78°C , 40 min; ii. TMSCl , Et_3N , -78°C , 20 min; (c) Hexanal , $\text{BF}_3 \cdot \text{OEt}_2$, CH_2Cl_2 , -78°C , 2 h; (d) i. $(\text{C}^t\text{Hex})_2\text{BBr}$, Et_3N , Et_2O , 0°C , 2.5 h; ii. Aldehyde **84-86** or hexanal , -78°C , 3h; iii. H_2O_2 , MeOH , pH 7 buffer, 0°C , 1 h.

Scheme 37 *Anti Aldol reactions with hexanal and simple aldehydes*

Gennari⁸¹ has shown that the $\text{BF}_3 \cdot \text{OEt}_2$ mediated thioester silylketene acetal addition to aldehydes gives high *anti:syn* ratios and good yields. It was originally envisaged that this methodology could be used to effect the C(7)-C(8) connection for

the synthesis of octalactin A. The development of a chiral Lewis acid would then be required to give the desired enantioselectivity.

Using the methodology developed by Gennari, the aldol reaction of thioester **88** with hexanal was carried out to give the *anti* aldol adduct **92** in 97% yield. Analysis of the 200 MHz ^1H NMR spectrum showed a >9:1 selectivity for the *anti* diastereomer^{*}. Despite giving an excellent chemical yield and good stereoselectivity the reaction proved to be extremely capricious in nature[§] and an alternative procedure was adopted to effect the *anti* aldol coupling.

The methodology of Masamune⁸² was used in conjunction with the work done by Gennari¹⁷ on aldol reactions with *E*-enol borinates, using $^c\text{Hex}_2\text{BBr}/\text{Et}_3\text{N}$ in order to seek more reliable reaction conditions.

Treatment of hexanal with 1.5 equivalents of the *E*(O)-enol borinate of thioester **88** gave the *anti* aldol adduct **92** in good yield (**Scheme 37**). Analysis of the 250 MHz ^1H NMR showed a high degree of diastereoselectivity ($\geq 95\%$) in favour of the *anti* aldol product (the *syn* diastereomer was undetected in the ^1H NMR of the crude reaction mixture).

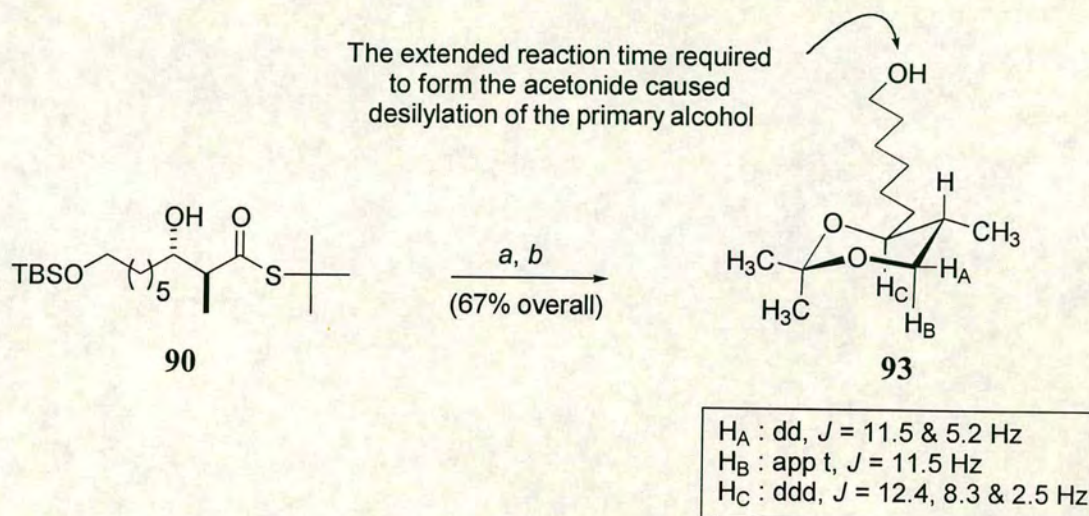
The same conditions were used with the simple aldehydes **84-86** to give the *anti* aldol adducts **89-91** in good yields (66-83%) and with a high degree of stereoselectivity in each case.

^{*} In most cases the *syn* and *anti* aldol adducts should be distinguishable by ^1H NMR. When in solution a β -hydroxy ketone exists in a chair-like conformation due to intramolecular hydrogen bonding. The long chain (initially of the aldehyde) adopts a favoured equatorial position and as a result the dihedral angle between the α and β hydrogens is $\sim 60^\circ$ for *syn* aldol adducts and $\sim 180^\circ$ for *anti* aldol adducts. Therefore the Karplus relationship predicts that the ^1H NMR vicinal coupling constant should be ~ 7 - 12 Hz for the *anti* adduct and ~ 3 - 5 Hz for the *syn* adduct. In practice a coupling constant of ~ 6 - 7 Hz is observed for the *anti* β -hydroxythioesters.

[§] The aldol reaction using a silyl ketene acetal gave no aldol products when used on more complex aldehydes.

2.3.2 Confirmation of Stereochemistry

The *anti* stereochemistry of the aldol adducts was based on the literature precedent, but was unambiguously determined by conversion to the acetonide **93** (Scheme 38).



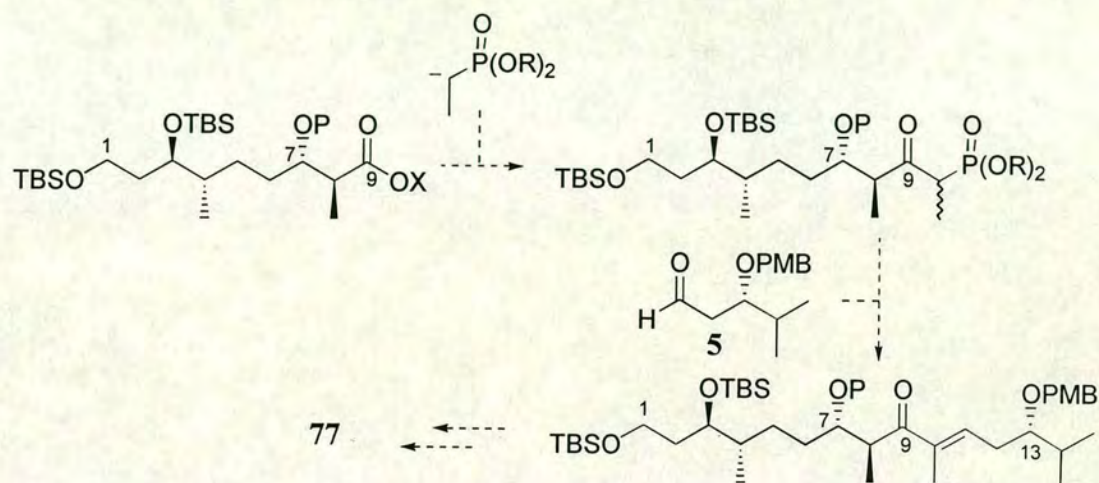
(a) LiBH_4 , THF, rt, 1.5 h; (b) Dimethoxypropane, $\text{TsOH} \cdot \text{H}_2\text{O}$, DMF, rt, 72 h.

Scheme 38 Confirmation of *anti* stereochemistry

Lithium borohydride reduction (LiBH_4 , THF, rt) produced the corresponding 1,3-diol (98% yield) the crude diol which was then converted to the acetonide **93** (68%, two steps). Decoupling experiments (^1H NMR, 600 MHz) to confirm the assignments, followed by analysis of the pertinent coupling constants thereby confirmed the stereochemistry of the starting aldol adduct **90**.

2.4 CARBON BACKBONE EXTENSION

It was necessary to extend the carbon backbone of the aldol adduct and produce the required enone **77**, an advanced intermediate in the synthesis of octalactin A. This could be achieved by displacement of the ester functionality with the lithiated anion of an alkyl phosphonate and introduction of the appropriate aldehyde in the HWE coupling (Scheme 39).



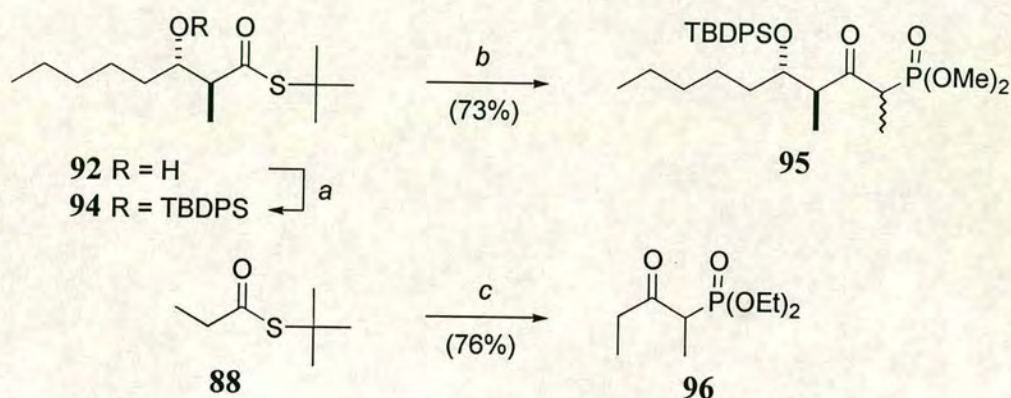
Scheme 39 Proposed synthesis of key intermediate **7**

2.4.1 Thioester Displacement

Thioesters have been used as intermediates in a number of important natural product syntheses. However, their use in synthesis has largely been limited to the generation of carboxylic acids,⁸³ esters,⁸⁴ lactones,⁸⁴ and β -ketoamides.⁸⁵ The potential for the use of thioesters in natural product synthesis has greatly increased recently due to a number of developments in aldol methodology, where particularly difficult aspects of stereocontrol have been tackled effectively. Chiral boron reagents developed by Gennari,¹⁸ and Masamune⁸² have been shown to give high levels of both diastereo- and enantio-control with thioester substrates. Similarly, in the development of new chiral Lewis acids for the catalytic asymmetric Mukaiyama acetate aldol reaction, many authors have concentrated on the use of thioester substrates.⁸⁶ Thus, new methodology for their synthetic development would be

particularly important not only for the synthesis of octalactin A, but for many other natural products containing related structural motifs.

In a recent paper, Mosset⁸⁷ identified a number of distinct routes to the synthesis of β -ketophosphonates. Of particular relevance to this work is the reaction of α -carbanionic alkylphosphonates with carboxylic acid esters and carboxylic acid chlorides. An extension of this strategy would be the reaction of α -carbanionic alkylphosphonates with (protected) thioesters **89-91**. This would then set up the desired β -ketophosphonates for the introduction of an appropriate aldehyde, and further chain extension.



(a) TBDPSCl, imidazole, DMF, rt, 18 h, (77%); (b) i. Dimethyl ethanephosphonate, ^tBuLi, DMPU, THF, -42 °C, 1 h; ii. thioester **94**, -78 °C, 20 min; (c) i. Diethyl ethanephosphonate, ⁿBuLi, THF, -78 °C, 1 h; ii. add to thioester in THF, -78 °C, 1h.

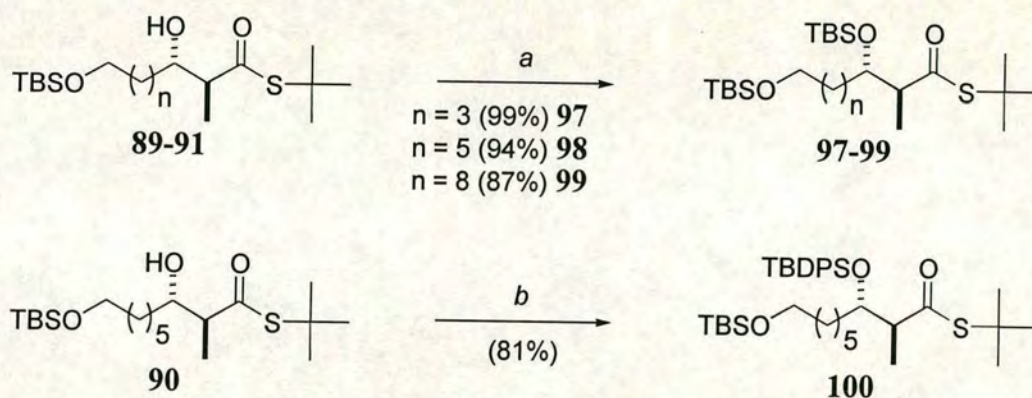
Scheme 40 Carbanionic displacement of simple thioesters

The displacement reaction was carried out using the lithiated anion of dimethyl ethanephosphonate with the ^tbutyldiphenylsilyl (TBDPS) protected *anti* aldol adduct **94**.⁸⁸ The β -ketophosphonate **95** was formed as a ~3:1 mixture of diastereomers in 73% yield (**Scheme 40**).⁶ The displacement reaction with ^tbutyl thiopropionate **88** using the lithiated anion of dimethyl ethanephosphonate under the same conditions was equally successful.

⁶ In this reaction and in subsequent displacements of this type, the relative stereochemistry α to the phosphonate was not assigned.

Although these reactions were initially conducted using $t\text{BuLi}$ in the presence of DMPU (1 eq.), it was later discovered that deprotonation by $n\text{BuLi}$ was just as effective, and that the addition of DMPU was not required. In general, the best results were obtained when the solution of the carbanion was added *via* cannula to a precooled solution of the thioester. It was also noted that the anion generated from dimethyl ethanephosphonate was considerably more sluggish in its reactions than its diethyl counterpart and generally required either a higher reaction temperature ($-42\text{ }^{\circ}\text{C}$ *c.f.* $-78\text{ }^{\circ}\text{C}$) or longer reaction times for the reaction to proceed to completion. Thus, the displacement reaction with t -butyl thiopropionate using the lithiated anion of diethyl ethanephosphonate was conducted (Scheme 40) to give **96** in 76% yield.

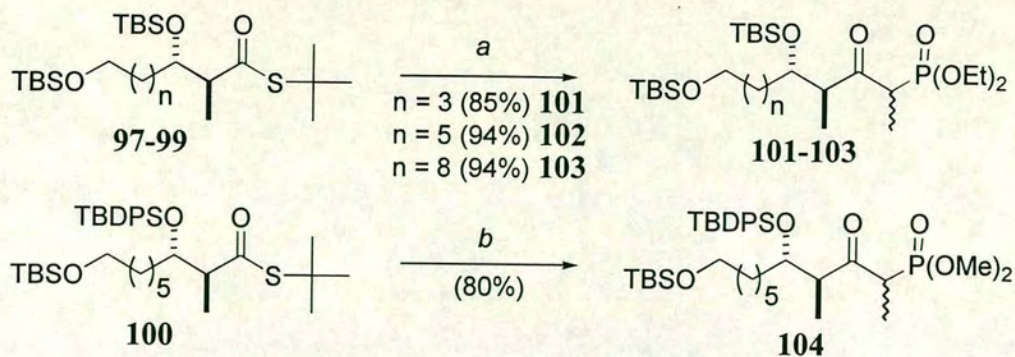
The β -hydroxythioesters **89-91** were protected as either their t -butyldimethylsilyl or t -butyldiphenylsilyl ethers (Scheme 41). This proceeded smoothly to give **97-99** and **100** respectively in excellent yields (81-99%).



(a) TBSCl, imidazole, DMF, rt, 24 h; (b) TBDPSCl, imidazole, DMF, rt, 18 h.

Scheme 41 Silylation of aldol adducts

The resultant protected aldol adducts **97-100** were converted to their corresponding β -ketophosphonates **101-104** (Scheme 42) using the methodology developed for the simple thioesters in good to excellent yield (80-94%).



(a) i. $n\text{-BuLi}$, THF, $-78\text{ }^{\circ}\text{C}$, 1 h; ii. add to thioester in THF, $-78\text{ }^{\circ}\text{C}$, 1 h; (b) i. $t\text{-BuLi}$, DMPU, THF, $-42\text{ }^{\circ}\text{C}$, 1 h; ii. thioester **100**, $-78\text{ }^{\circ}\text{C}$, 20 min.

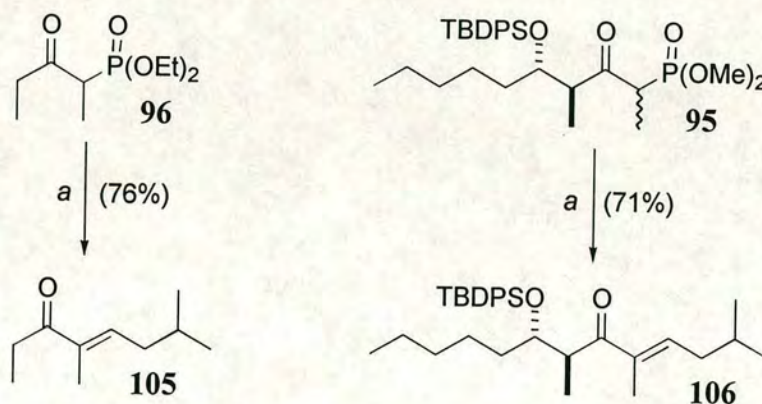
Scheme 42 Carbanionic displacement of aldol adducts

As with aldol adduct **94**, the reactions of dialkyl ethanephosphonate anions with the aldol adducts **97-100** were found to produce a $\sim 3:1$ ratio of diastereomers in every case. These were inseparable by flash chromatography and as it was anticipated that both diastereomers would form the desired *E*-trisubstituted enones under HWE conditions no effort was made to separate them.

The displacement is also possible in the presence of PMB ethers and alkyl ethers and from these results it can be seen that a range of protecting groups can be tolerated under these reaction conditions.⁸⁸

2.4.2 Horner Wadsworth Emmons Coupling

The Horner Wadsworth Emmons (HWE) reaction between alkyl phosphonates and aldehydes is frequently used for the synthesis of di- and tri-substituted double bonds.⁸⁹ Recently there have been several mild conditions developed for the HWE reaction between β -ketophosphonates and aldehydes,^{46,90} making this reaction particularly suited to the synthesis of complex natural products, where it has found use both in fragment coupling,⁹¹ and macrocyclisation reactions.⁹² Reaction of simple β -ketophosphonate **96** using the mild activated barium hydroxide conditions of Paterson as discussed in **Chapter 1**, and with isovaleraldehyde as a model for aldehyde **5**, gave the tri-substituted enone **105** in 76% yield and >95% *E/Z* selectivity^f (**Scheme 43**).



(a) i. $\text{Ba}(\text{OH})_2 \cdot 8\text{H}_2\text{O}$, THF (aq.); ii. Isovaleraldehyde, rt, 18 h.

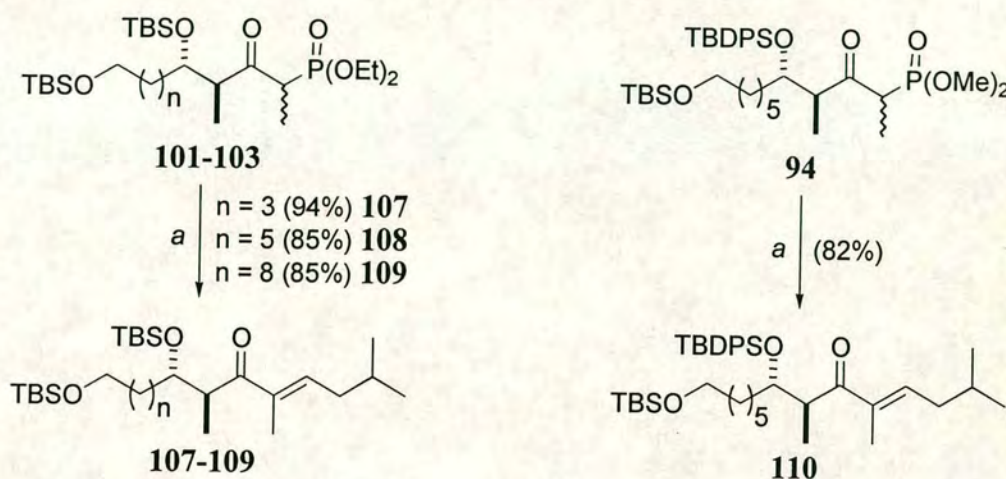
Scheme 43 HWE reaction with simple β -ketophosphonates

The HWE reaction was attempted on **95** with isovaleraldehyde and both diastereomers of the phosphonate were converted to the α,β -unsaturated ketone **106** (**Scheme 43**) in 71% yield. Analysis of the 250 MHz ^1H NMR showed it to be a single geometrical isomer and a single diastereomer, thereby confirming that no

^f The formation of the other geometrical isomer (*Z*) was not observed in the ^1H or ^{13}C NMR spectra of either of these two compounds. The *E*-geometry of the alkene was assigned on the basis of precedent.

epimerisation (of the *anti* stereochemistry derived from the aldol reaction) had occurred during either the carbanionic displacement or in the HWE reaction itself.^f

Using the conditions optimised for the above substrates the HWE reaction as carried out on the more functionalised β -ketophosphonates **101-104** and **94** to give the α,β -unsaturated ketones **107-110** (Scheme 44) in good to excellent yields (82-94%) and with *E/Z* selectivity >95%.[†]



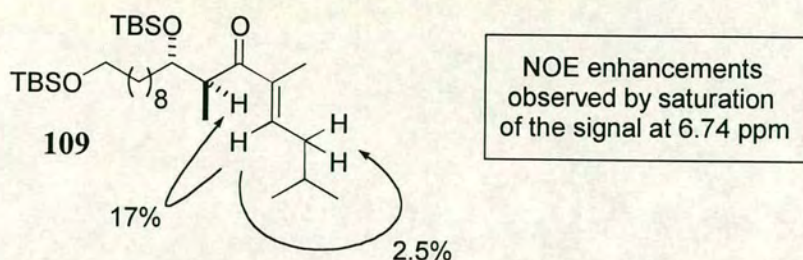
(a) i. $\text{Ba(OH)}_2 \cdot 8\text{H}_2\text{O}$, THF (aq.); ii. Isovaleraldehyde, rt, 18 h.

Scheme 44 HWE couplings with more complex β -ketophosphonates

As discussed above, all of the HWE reactions with the more complex β -ketophosphonates proceeded smoothly to give the enones as single diastereomers (again confirming that no epimerisation had occurred in the displacement or HWE reactions) and all with the *E*-trisubstituted alkenes as the sole products.

However, as the enone system is expected to be quite rigid it was proposed that some simple nuclear Overhauser effect (NOE) measurements would confirm the expected stereochemistry.

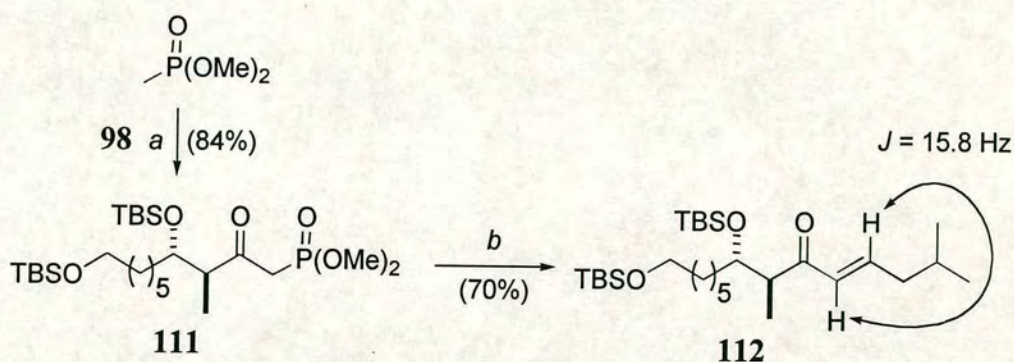
[†] No traces of any diastereomeric or geometric isomers could be detected in the crude ^1H NMR spectra.



Scheme 45 NOE enhancements for enone **109**

NOE measurements were taken from saturation of the signal at $\delta = 6.74$ (^1H NMR, 250 MHz, CDCl_3) assigned to the vinylic proton in **109**. Enhancements (+17 and +2.5% respectively) were observed at $\delta = 3.50$ (CHCHMeC=O) and $\delta = 2.20$ ($\text{CH}_2\text{CH=C}$). A large, positive NOE enhancement due to saturation of the allylic methyl signal at $\delta = 1.93$ would be expected at $\delta = 6.74$ in the related *Z*-isomer. No such NOE effect was observed.

Further evidence for the formation of the *E*-isomer during this reaction comes from the HWE reaction between the β -ketophosphonate **111** (formed by reacting the lithiated anion of dimethyl methanephosphonate with the protected aldol adduct **98**) and isovaleraldehyde (**Scheme 46**).



- (a) i. $^n\text{BuLi}$, THF, -78°C , 1 h; ii. add to thioester **98** in THF, -78°C , 1 h;
 (b) i. $\text{Ba}(\text{OH})_2 \cdot 8\text{H}_2\text{O}$, THF (aq.); ii. Isovaleraldehyde, rt, 18 h.

Scheme 46 Synthesis of a di-substituted enone

A di-substituted double bond was thus generated to give **112** in 70% yield (unoptimised). The *E*-geometry of this double bond was confirmed by the large ^1H NMR vicinal coupling constant ($J = 15.8$ Hz).

2.5 APPROACH TO THE CYCLISATION

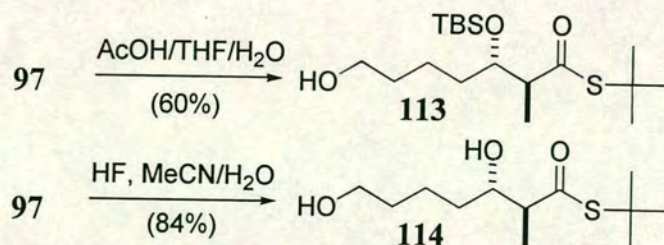
In order to conduct an Evans Tishchenko intramolecular coupling in the manner described in Section 2.1 (Scheme 31) it was necessary to modify the model HWE reaction products to give substrates suitable for cyclisation.

This could be done by either deprotection of the primary hydroxyl, oxidation to the aldehyde and deprotection, or by total deprotection and selective oxidation^{f,93}

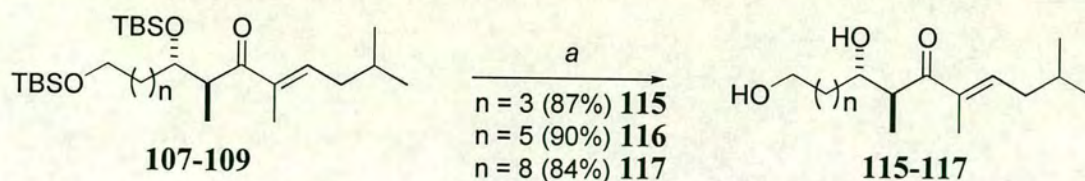
2.5.1 Deprotection of the HWE Adducts

The desilylation of primary and secondary hydroxyls with HF-based reagents has been shown to be milder than the conditions required for TBAF removal of TBS groups.⁹⁴ Therefore, the HWE adducts **97-99** were smoothly deprotected to give the corresponding 1,n-diols **105-107** using 40% aqueous HF in MeCN/THF^y (Scheme 47) in excellent yield (84-90%) with no epimerisation of the centre α to the ketone.

^f Initial investigations into the deprotection of β -hydroxy thioester **97** showed that either the primary group could be removed selectively (**97**→**113**) or both silyl groups (**97**→**114**) could be removed simultaneously thereby making both strategies viable options.



^y This particular solvent system was chosen due to the inherent insolubility of the HWE adducts **97-99** in aqueous acetonitrile.

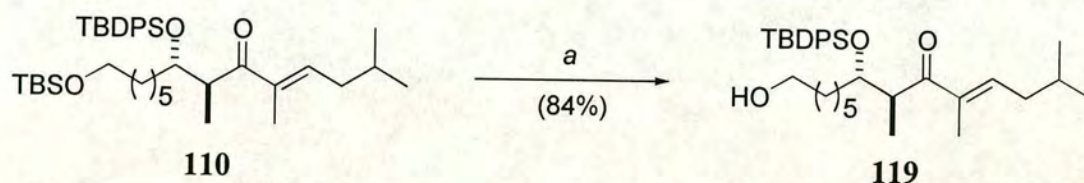


(a) 40% aq. HF, MeCN/THF, rt, 50 min.

Scheme 47 Total deprotection

Care was taken in the monitoring of these reactions as extended reaction times (≥ 1 h) or improper quenching of the reaction mixtures resulted in the disappearance of the desired products. The formation of an unwanted product resulting from unexpected HF addition to the double bond was observed after an extended reaction with **108** and also when the crude reaction mixture was left in the refrigerator overnight^ξ.

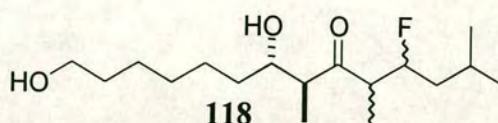
The HWE adduct **110** was selectively deprotected using AcOH/THF/H₂O (3:1:1) and gave the alcohol **109** in excellent yield (84%) as a single diastereomer (Scheme 48).



(a) AcOH/THF/H₂O, rt, 4 h.

Scheme 48 Selective deprotection

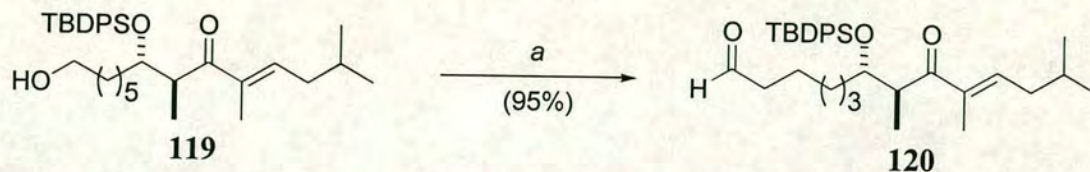
^ξ Addition product **118** was isolated as the sole product in a reaction with **108** left for 3 h. 200 MHz ¹H NMR analysis gave the structure:



No appreciable amount of the diol **116** was formed although the reaction was carefully monitored to minimise removal of the TBDPS group.

2.5.2 Oxidation

Oxidation of alcohol **119** was performed with IBX using the conditions developed for the simple alcohols in Section 2.2.2.



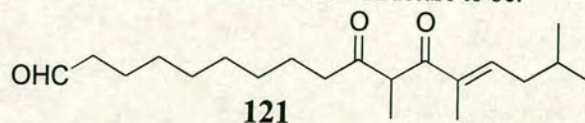
(a) IBX, THF/DMSO, rt, 3 h.

Scheme 49 Oxidation using IBX

The reaction proceeded smoothly to give the aldehyde **120** in excellent yield (95%) and as a single diastereomer (Scheme 49). Attempted desilylation of this compound using TBAF to produce the unprotected β -hydroxy enone caused decomposition and a multi spot tlc perhaps due to the slightly basic nature of this reagent. Lack of material and the availability of a shorter route (total deprotection, selective oxidation), precluded any further investigation into this sequence of reactions.

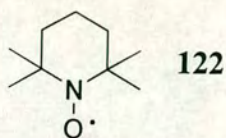
It was hoped that using just one equivalent of IBX a selective oxidation could be performed on each of the diols **115-117** to give the desired aldehydes. Oxidation of **117** with one equivalent of IBX indeed produced the desired aldehyde but a substantial amount of the doubly oxidised product **121**[‡] were observed and this method was not further developed.

[‡] The doubly oxidised product arose from unselective oxidation of both the primary and secondary alcohols. Analysis of the 200 MHz ¹H NMR showed the structure to be:



2.5.3 Selective Oxidation

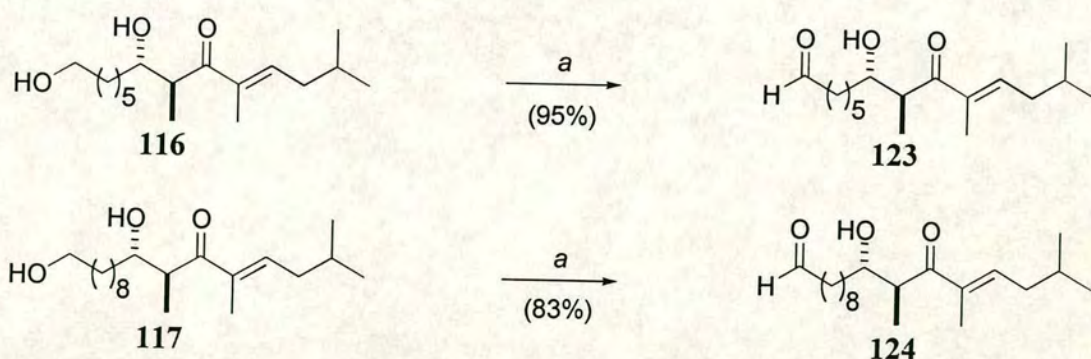
TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy, free radical) **122** (Scheme 50) has been used effectively as an efficient catalyst for the selective oxidation of primary hydroxy groups in primary/secondary diols,⁹³ and has been employed in the synthesis of a number of natural products.⁹⁵



TEMPO (2,2,6,6-Tetramethyl-1-piperidinyloxy, free radical)

Scheme 50 TEMPO

TEMPO has also been used in the oxidation of optically active α -amino and alkoxy alcohols with no racemisation⁹⁶ and is regarded as an extremely mild oxidising agent. Any possible over-oxidation to the acid can be minimized by rapid stirring.⁹⁵ For these reasons it was decided to use TEMPO to facilitate the required selective oxidation.



(a) TEMPO, $n\text{Bu}_4\text{NCl}$, NaOCl , NaBr , sat. NaHCO_3 (aq.), sat. NaCl (aq.), CH_2Cl_2 , rt, 4 h.

Scheme 51 Selective oxidation using TEMPO

Using modified Skarzewski⁹³ conditions[¶] the 1,7- and 1,10-diols **116** and **117** were selectively oxidised to the desired aldehydes in excellent yield (95% and 83% respectively) (**Scheme 51**).

The aldehydes **123** and **124**, whilst being fairly stable to silica gel, once chromatographed, rapidly decomposed to a complex mixture of products.[‡]

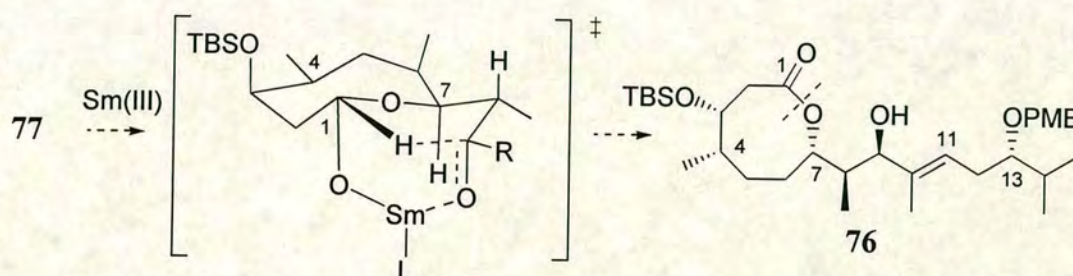
[¶] It should be noted that the conditions for the oxidation were optimised for the substrates concerned and are not necessarily optimum for other cases.

[‡] The crude aldehydes were slightly orange in colour (presumably due to residual TEMPO) and were substantially more stable to autooxidation than the purified products. This phenomenon has been reported on a number of other occasions.⁹⁵

2.5.4 Evans-Tishchenko Reactions

Recent reports of samarium catalysed cyclisation reactions of keto-aldehyde substrates have focused on the pinacol-based formation of 5- and 6-membered rings.^{51,59,97}

As discussed in **Chapter 1**, the Evans-Tishchenko reaction typically requires catalysis by 15-30 mol% of a SmI₂ solution in THF, and results in the directed reduction of a β -hydroxy ketone to give an *anti* 1,3-diol with the selective formation of a monoester (*anti:syn* >95:5).⁶³



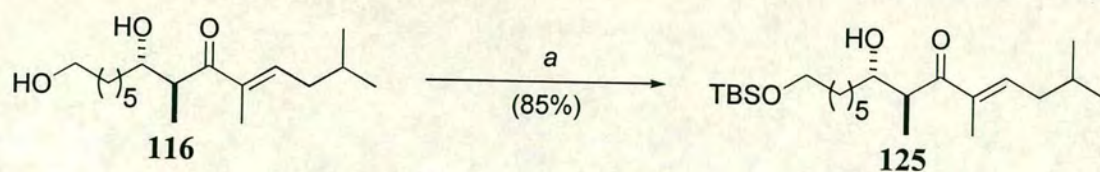
Scheme 52 Proposed Sm(III) catalysed cyclisation

The proposed mechanism invokes an intramolecular hydride transfer from an intermediate hemiacetal *via* a tricyclic transition state similar to that shown in **Scheme 52** and is thought to be catalysed by a SmI₃•SmI(RCHO)₂ pinacol adduct which is either preformed, or generated *in situ*.

Whilst there have been a number of Evans-Tishchenko couplings used in the synthesis of natural products,^{64,65} there are no reported examples of an Evans-Tishchenko reaction using a β -hydroxy enone as would be required for the synthesis of **76** (**Scheme 52**).

It was thought that non-stereoselective 1,2- or 1,4-reduction may interfere with the Evans-Tishchenko reaction and it was therefore decided to conduct the reaction on a substrate, **125**, related to the cyclisation precursors **123** and **124**.

The feasibility of the intramolecular version of the reaction could then be assessed.

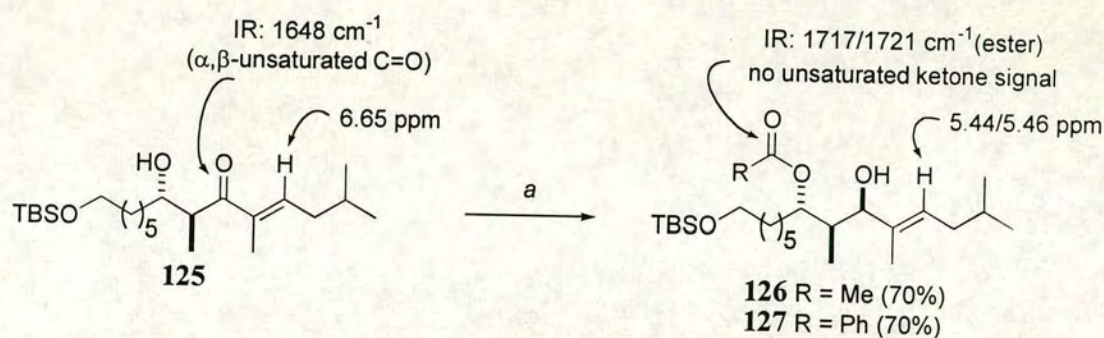


(a) TBSCl, imidazole, DMF, rt, 4 h.

Scheme 53 Selective silylation of the primary hydroxyl

The primary hydroxyl of the diol **116** was selectively protected as its TBS ether using TBSCl/imidazole to give β -hydroxy ketone **125** (85%) (**Scheme 53**).

Evans-Tishchenko reactions with either excess benzaldehyde, or acetaldehyde, on protected β -hydroxy enone **125** afforded the *anti*^y diol monoesters **126** and **127** each in 70% yield as single diastereomers (**Scheme 54**).



(a) PhCHO or MeCHO (4 eq.), SmI₂ (1M in THF, 60 mol%), THF, 0 °C, 10 min.

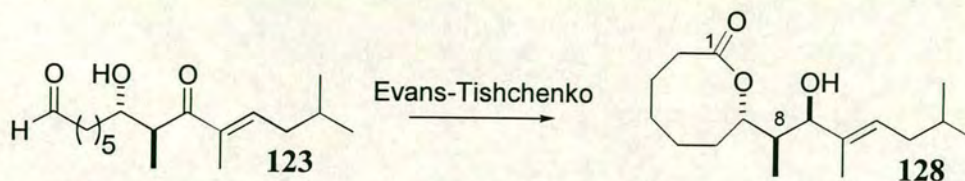
Scheme 54 Evans-Tishchenko reactions with acetaldehyde and benzaldehyde

These are the first examples of Evans-Tishchenko reactions with β -hydroxy enones thus considerably extending the methodology encouraging an attempt of the reaction with the cyclisation precursors **123** and **124**.

^y The *anti* stereochemistry was assigned on the basis of precedent.^{63,65,98}

2.5.5 Intramolecular Evans-Tishchenko Cyclisation

A range of conditions as well as other samarium based catalysts were studied, the results of which are summarised in Table 3.



Entry	Catalyst	No of eq.	Temp	Product	Yield ^d
1	SmI ₂	30 mol%	0 °C	complex mixture	—
2	SmI ₂	1.0	0 °C	complex mixture	—
3	SmI ₂	30 mol%	-25 °C	complex mixture	—
4	SmI ₂ /PhCHO	30 mol%	-25 °C	epimeric at C(8)	30%
5	SmI ₂ /PhCHO	60 mol%	0 °C	epimeric at C(8)	25%
6	SmI ₂ /PhCHO	1.0	0 °C	epimeric at C(8)	26%
7	SmI ₃	1.0	RT	reduction at C(9)	—
8	SmI ₂ O ^t Bu ^a	1.0	0 °C	complex mixture	—
9	Sm(OTf) ₃ ^b	1.0	RT	no reaction ^c	—

a) Formed by reaction of a solution of samarium (II) iodide in THF with 1 equivalent of ^tBuOH;

b) Commercially available, purchased from Aldrich Chemical co.; c) Although no reaction was observed, the crude ¹H NMR showed a shift in the signals due to the aldehydic and vinylic protons; d) Isolated yield after flash chromatography.

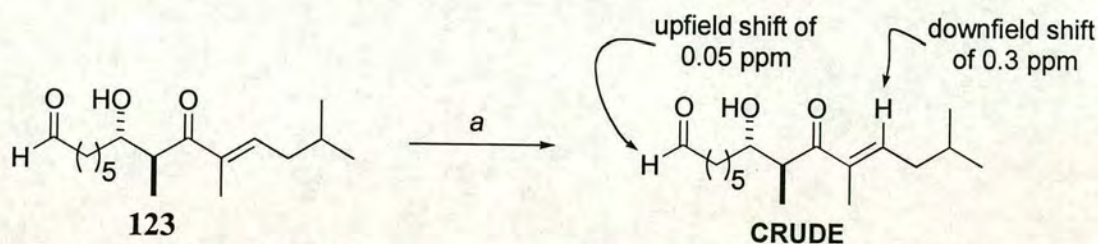
Table 3 Intramolecular Evans-Tishchenko coupling

Initially, the use of just samarium (II) iodide alone with varying concentrations and modes of addition was examined. All of the conditions studied produced a complex mixture of products. This is probably due to the pinacolisation

of the cyclisation precursor although no evidence to suggest this was obtained.⁵⁹ As the reaction is believed to involve a samarium (III) catalyst, other reagents of this type were investigated to study their suitability in the coupling.

Samarium (III) iodide (produced by treatment of samarium metal and excess iodine in THF) gave no cyclisation product (aldehyde signal still present) but a significant change in the chemical shift of the C(11) vinylic proton ($\delta=6.62$ ppm (**123**) \rightarrow $\delta=5.44$ ppm (**128**)) indicated reduction of the enone functionality in the crude ^1H NMR.

Reaction of aldehyde **123** appeared not to undergo cyclisation in the presence of samarium (III) triflate. However, analysis of the crude ^1H NMR showed there to be significant shifts in the signals due to the aldehydic and vinylic protons (**Scheme 55**). An upfield shift of 0.05 ppm for the aldehydic proton and a 0.3 ppm downfield shift for the vinylic proton were observed suggesting chelation to aldehyde and the enone functionalities in the molecule. Whilst no signal for the vinylic proton in aldehyde **123** remained, the aldehydic signal was still present perhaps suggesting a higher degree of chelation to the enone functionality.



(a) $\text{Sm}(\text{OTf})_3$, THF, rt, 15 min.

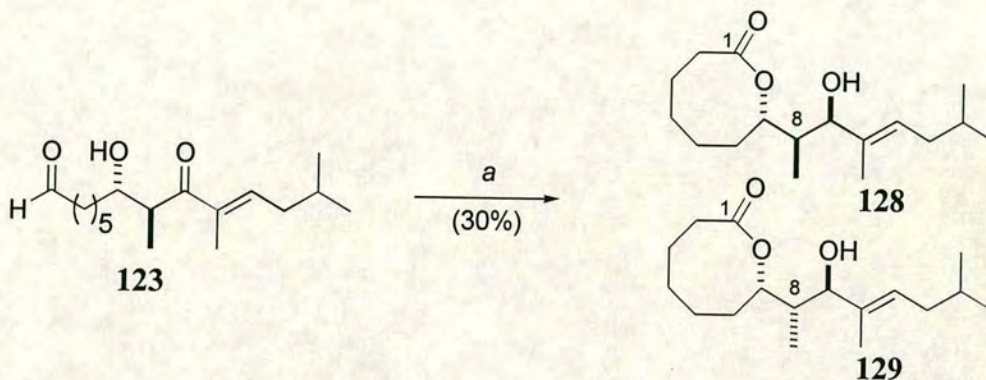
Scheme 55 Reaction of aldehyde **123** with $\text{Sm}(\text{OTf})_3$

It was found that by pre-forming the pinacol adduct in THF and adding the aldehyde as a solution in THF slowly and dropwise gave the best results.⁷

⁷ The conditions for the work-up of these reactions have also been studied, with potassium sodium tartrate (Rochelle's) salt found to be the optimum solution for removing the samarium residues.⁹⁹

When the intramolecular reaction was attempted on **123** using the preformed Sm(III)/PhCHO catalyst, the reaction appeared to have proceeded smoothly by the observation of a slightly higher non-uv active R_f spot in the tlc (indicating reduction of the enone system) and analysis of the crude 200 MHz ^1H NMR.

However, high field ^1H NMR (600 MHz) confirmed the formation of a 1:1 mixture of two inseparable diastereomers **128** and **129** (30% combined yield) (Scheme 56).



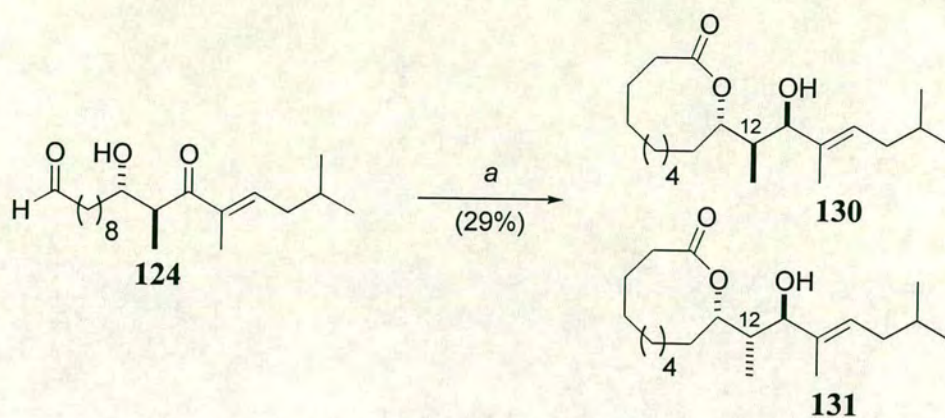
(a) PhCHO/ SmI_2 (premixed, 0.4 M in THF, 30 mol%), THF, 0 °C, 10 min.

Scheme 56 Evans-Tishchenko cyclisation

Coupling occurred smoothly to give the lactone despite giving the two diastereomers **128** and **129**.

Other possible reactions; Tishchenko, or pinacol coupling onto the C(9) carbonyl itself can be excluded on the basis of the ^1H NMR data for C(7)H ($\delta=4.86$ -4.81, m) and C(9)H ($\delta=3.88$ -3.85, 0.5H, m, & $\delta=3.84$ -3.91, 0.5H, m), which correlates extremely well with the data for acetate **126**. A significant change in the chemical shift of the C(11) vinylic proton ($\delta=6.62$ ppm (**123**) \rightarrow $\delta=5.47$ ppm (**128/129**)) also confirmed reduction of the enone functionality.

Using the optimum conditions as discussed above (30 mol% $\text{SmI}_2/\text{PhCHO}$, 0 °C, THF, 10 min), the aldehyde **124** was converted to the 11-membered lactone (Scheme 57).



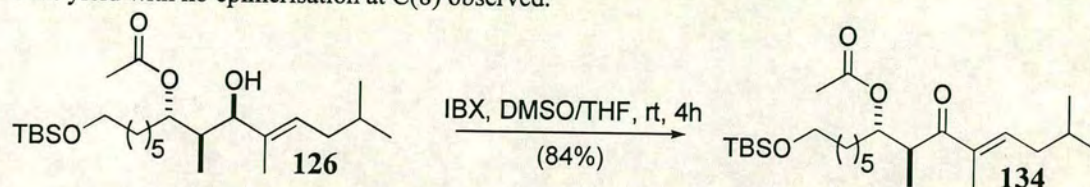
(a) PhCHO/SmI₂ (premixed, 0.4 M in THF, 30 mol%), THF, 0 °C, 10 min.

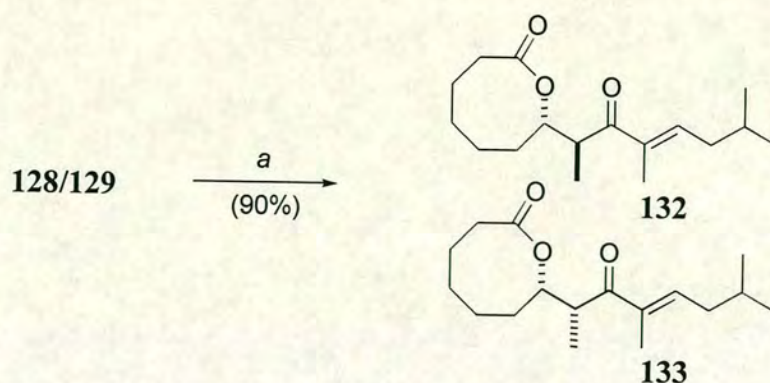
Scheme 57 *Evans-Tishchenko cyclisation*

Unfortunately, the reaction, as before, caused the formation a 1:1 ratio of two inseparable diastereomers **128** and **129** (29% combined yield) attributed to epimerisation at C(12) prior to cyclisation.

Oxidation of the diastereomeric mixture **128** and **129** with *o*-iodoxybenzoic acid (IBX) cleanly afforded two diastereomers **132** and **133** (90% combined yield), which were now readily separable by chromatography⁹ (Scheme 58).

⁹ **126** was oxidised (IBX, DMSO/THF, rt) to give **134**. The enone functionality was regenerated in 84% yield with no epimerisation at C(8) observed.





(a) IBX, THF/DMSO, rt, 3 h.

Scheme 58 Oxidation of Evans-Tishchenko products

This indicated that stereoselective hydride transfer had occurred during cyclisation (the *anti* stereochemical assignment at C(9) has been made on the basis of precedent⁶³⁻⁶⁵) and that loss of stereochemical integrity was perhaps due to epimerisation at C(8/12) prior to cyclisation.[†] Further evidence for this was found when the ¹H NMR spectrum of the reaction mixture prior to chromatography was examined and it was observed that the unreacted aldehydes **123** and **124** were now also a mixture of diastereomers. Unfortunately, isolation of these unreacted aldehydes proved impossible, due to their instability.

With hindsight, the approach to the initial investigation of the construction of the octalactin A framework model using unfunctionalised ring precursors may have required the most demanding mode of cyclisation. In his approach to the octalactins, Andrus has shown that an unfunctionalised C(1)-C(9) precursor gives only a 24% yield of the lactone under modified Keck-Boden macrolactonisation conditions, whereas the TBS protected, functionalised C(1)-C(9) precursor cyclises in 81% yield under the same conditions.⁶⁶ This has been ascribed to a predisposition of the fully functionalised substrate to adopt a chair-boat conformation favourable to cyclisation. It was hoped that when the fully functionalised precursor **77** was subjected to the Evans-Tishchenko conditions, a similar increase in yield in the cyclisation reaction

[†] A similar result has been observed in a titanium-mediated aldol-Tishchenko reaction.¹⁰⁰

would be observed, and that an enhanced rate of cyclisation relative to that of competing epimerisation at C(8/12) would be seen (as seen with the stereoselective reduction of β -hydroxy enone **125**).

A convergent approach to the carbon framework of octalactin A **1** as well as the synthesis of a 11-membered lactone analogue has been demonstrated and should allow a highly stereocontrolled synthesis of the key intermediate **76** which will be discussed later in detail in **Chapter 4**.

The synthesis of the unfunctionalised lactones relied upon a novel samarium mediated cyclisation strategy.⁶⁹ This synthetic strategy should allow for a flexible approach towards the synthesis of the octalactins that might be used to investigate the structure-activity relationship of this marine metabolite. The synthesis of analogues closely related to octalactin A may be used to help determine a more active structure and the area still remains of interest to the Hulme group.

RESULTS AND DISCUSSION PART 2

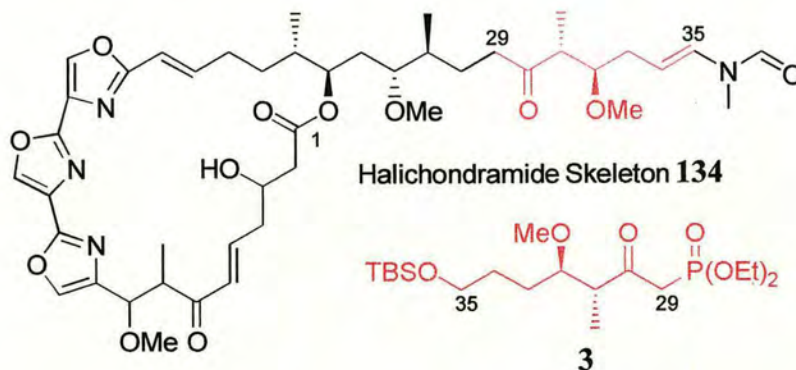
CHAPTER 3

SYNTHESIS OF THE C(29)-C(35) SECTION OF THE
HALICHONDRAAMIDE BACKBONE

3.1 DEVELOPMENT OF METHODOLOGY

The investigations into the *anti* aldol reaction and subsequent manipulations as discussed in **Chapter 2** prompted the demonstration of the general applicability of this methodology. This stereochemical pattern is abundant in many natural products and the methodology developed in **Chapter 2** is a useful extension by which these *anti* aldol adducts may be further manipulated.

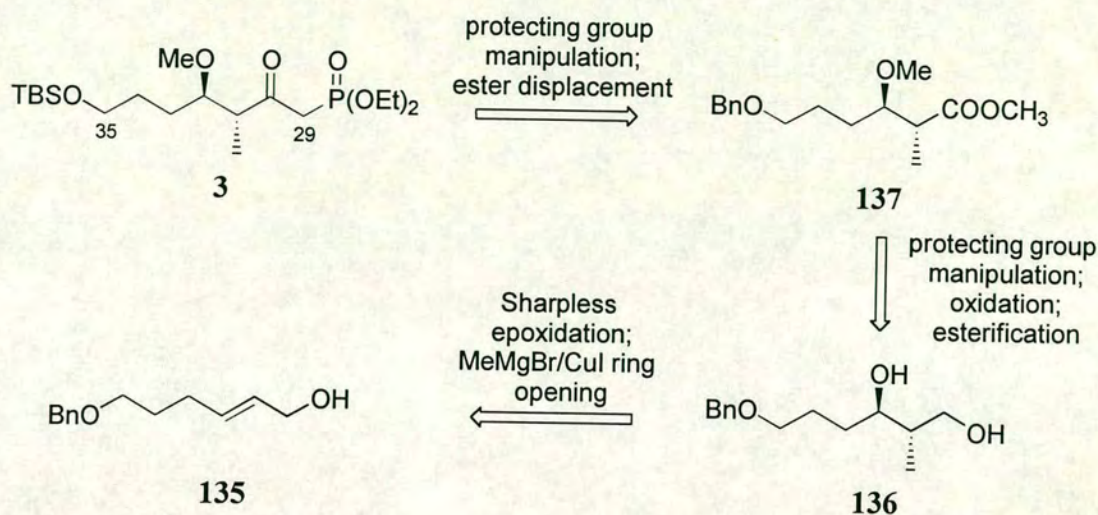
In order to demonstrate the utility of this methodology it was decided to synthesise racemic β -ketophosphonate **3** which has been used by Pattenden¹⁰¹ as the C(29)-C(35) section of the halichondramide backbone **134** (**Scheme 59**).



Scheme 59 Halichondramide and Pattenden's C(29)-C(35) fragment

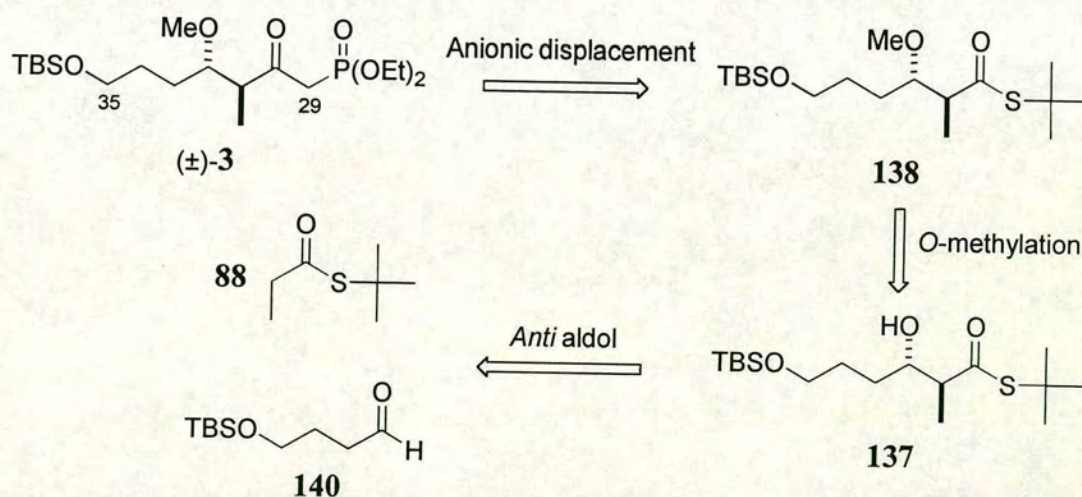
Pattenden's synthesis started from the known allylic alcohol **135**.¹⁰² Sharpless epoxidation was followed by ring opening to give the 1,3-diol **136** with the required *anti* stereochemistry. Protecting group manipulations and adjustment of the oxidation state gave the ester **137**. Further protecting group interconversion and

displacement of the ester using the anion derived from diethyl methanephosphonate provided **3** (10 steps, 12% overall yield from **135**).



Scheme 60 Pattenden's C(29)-C(35) fragment synthesis

A retrosynthetic analysis based on the methodology developed in **Chapter 2** is shown in **Scheme 61**.



Scheme 61 Retrosynthetic analysis for (±)-**3**

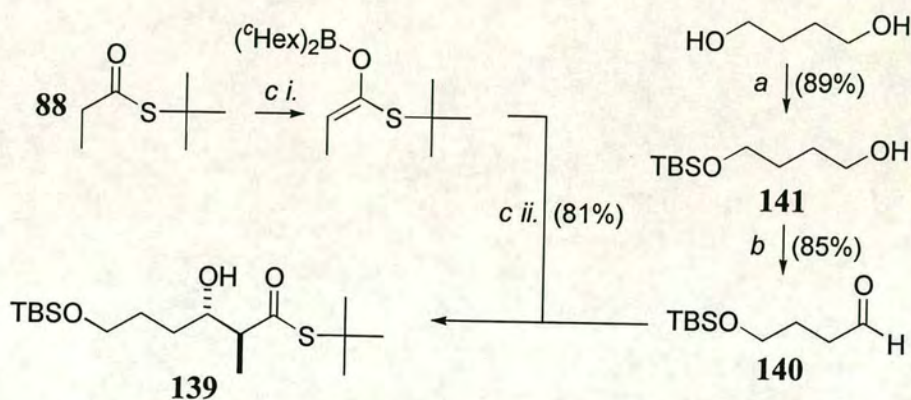
Anionic displacement in a similar fashion to Pattenden's synthesis reveals the β -methoxythioester **138**. This would be synthesised through methylation of the *anti*

aldol adduct **139**, derived from the *anti* aldol reaction of aldehyde **140** and the *E*-(O)-enol borinate of thioester **88** (Scheme 61).

3.2 ANTI ALDOL COUPLING

The aldehyde **140** was synthesised in two steps from butane-1,4-diol using the conditions discussed in Section 2.2.1 and 2.2.2. The diol was monoprotected as its *t*-butyldimethylsilyl ether (NaH, TBSCl, THF, rt, 1.5 h), giving **141** (89% yield), followed by oxidation (IBX, DMSO/THF, rt, 1 h) to the aldehyde in 85% yield.

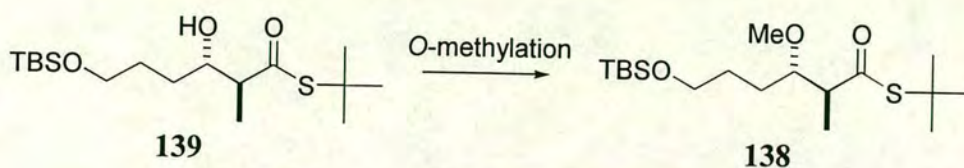
Enolisation of *t*-butyl thiopropionate **88** with Et₃N and ^cHex₂BBr and reaction with aldehyde **140** generated the *anti* aldol adduct **139** in 81% yield as a single diastereomer (Scheme 62).



(a) i. NaH, THF, rt, 40 min; ii. TBDMSCl, rt, 1 h; (b) IBX, THF/DMSO, rt, 1.5 h; (c) i. (^cHex)₂BBr, Et₃N, Et₂O, 0 °C, 2.5h; ii. **140**, -78 °C, 3h; iii. H₂O₂, MeOH, pH 7 buffer, 0 °C, 1 h.

Scheme 62 *Anti aldol coupling*

Subsequent methylation of the free hydroxyl proved to be more difficult than was first expected. A variety of reaction conditions were tried and the results are summarised in Table 4.



Entry	Conditions	Product	%Yield ^{a)}
1	^t BuOK, MeI, THF, rt	no reaction	—
2	Ag ₂ O, MeI, MeCN, 81 °C	no reaction	—
3	CH ₂ N ₂ , SiO ₂ , Et ₂ O, 0 °C to rt	no reaction	—
4	NaHMDS (0.5 M solution in toluene), MeI, THF, -78 °C, 20 min	<p style="text-align: center;">142</p>	42%
5	KHMDS (0.5 M solution in toluene), MeI, THF, -78 °C, 20 min	<p style="text-align: center;">143</p>	40%
6	Me ₃ O ⁺ BF ₄ ⁻ (1.6 eq.), Proton-Sponge [®] (1.5 eq.), CH ₂ Cl ₂ , rt, 1 h	<p style="text-align: center;">138</p>	25%
7	Me ₃ O ⁺ BF ₄ ⁻ (3.8 eq.), Proton-Sponge [®] (4.0 eq.), CH ₂ Cl ₂ , rt, 1 h	<p style="text-align: center;">138</p>	94%

a) Isolated yield after flash chromatography.

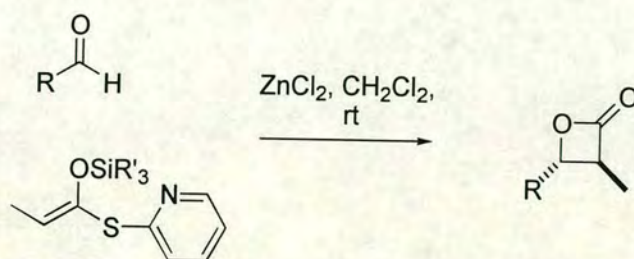
Table 4 *O*-methylation of aldol adduct 139

Initial reactions with methyl iodide and silver oxide with a variety of solvents, temperatures and using a vast excess (10-20 eq.) of methyl iodide gave no reaction, allowing the recovery of unreacted starting material. The diazomethane conditions of Ohno¹⁰³ (CH₂N₂, SiO₂, Et₂O, 0 °C to rt) gave no reaction either, allowing the recovery of unreacted aldol adduct 139.

It was thought that the use of sodium hydride might cause displacement of the thioester and was therefore avoided. The use of NaHMDS and KHMDS with methyl iodide in an attempt to methylate the free hydroxyl, produced some interesting results.

Reaction of the aldol adduct with NaHMDS/MeI at -78 °C produced the eliminated product 142 as the major product (42% yield). (The stereochemistry of the

double bond, whilst thought to be the thermodynamically favoured *E*-isomer, was not confirmed.) However, on treating the aldol adduct **139** with KHMDS/MeI the *trans*- β -lactone **143** was isolated as the major product and as a single diastereomer. Whilst being an interesting result it is not unprecedented. A recent report by Romo¹⁰⁴ has shown that β -lactones can be produced by the reaction of thiopyridyl ketene acetals and aldehydes in a tandem Mukaiyama aldol-lactonisation (TMAL) reaction (Scheme 63).

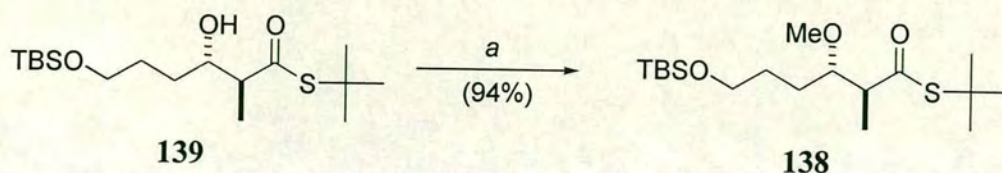


Scheme 63 TMAL reaction of thiopyridyl ketene acetals and aldehydes

Several structurally and biologically interesting natural products containing β -lactone rings have been isolated recently including the ebelactones, tetrahydrolipstatin and belactin B.¹⁰⁵ There are however, a limited number of direct and general methods for the preparation of β -lactones stereoselectively.¹⁰⁴

The development of this methodology is, unfortunately, beyond the scope of this thesis and the reaction was not further investigated.

Methylation of the secondary hydroxyl was finally achieved using Meerwein's salt ($\text{Me}_3\text{O}^+\text{BF}_4^-$) in the presence of Proton-Sponge[®] (Aldrich) to give protected thioester **138** in a 94% yield (Scheme 63).¹⁰⁶ Whilst initial reactions with 1.0-1.5 equivalents of the methylating agent produced the desired product (Table 4, entry 6), it was found that using a large excess (4 equivalents) of the reagents was optimum (Table 4, entry 7) and gave complete conversion.

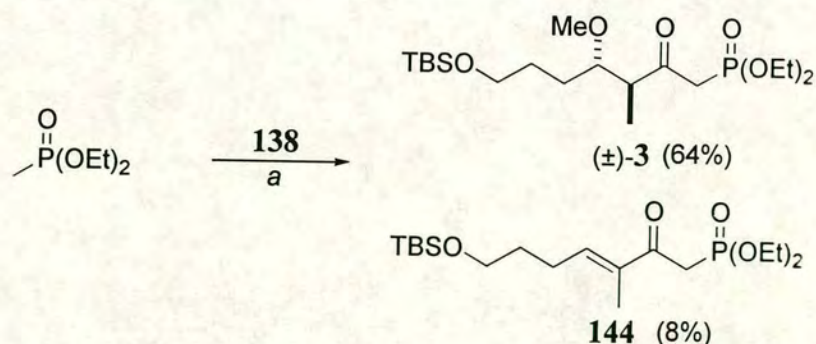


(a) $(\text{MeO})_3^+\text{BF}_4^-$, Proton Sponge[®], CH_2Cl_2 , RT, 1 h

Scheme 64 *O*-methylation of **139** with Meerwein's salt

3.3 PHOSPHONATE DISPLACEMENT

Phosphonate displacement of the thioester was carried out using two equivalents of the lithiated anion (formed by treatment of diethyl methanephosphonate at -78°C with $n\text{BuLi}$) using the conditions discussed in **Chapter 2**. A previously unobserved minor impurity **144**, formed by elimination of methanol from β -ketophosphonate (\pm)-**3**, was noted in the ^1H NMR of the crude reaction mixture. (As with the elimination product **142** the stereochemistry of the double bond in **144** was not confirmed but was thought to be the thermodynamically favoured *E*-isomer.) However, this impurity was found to be readily separable by HPLC allowing the isolation of (\pm)-**3** in 64% yield (**Scheme 65**).



(a) i. $n\text{BuLi}$, THF, -78°C , 1 h; ii. add to thioester **138** in THF, -78°C , 1 h.

Scheme 65 Carbanionic displacement of the thioester **138**

The synthesis was successfully completed giving (\pm)-**3** in 5 steps with an overall yield of 37%, which compares extremely favourably with the previous synthesis.

CHAPTER 4

TOTAL SYNTHESIS

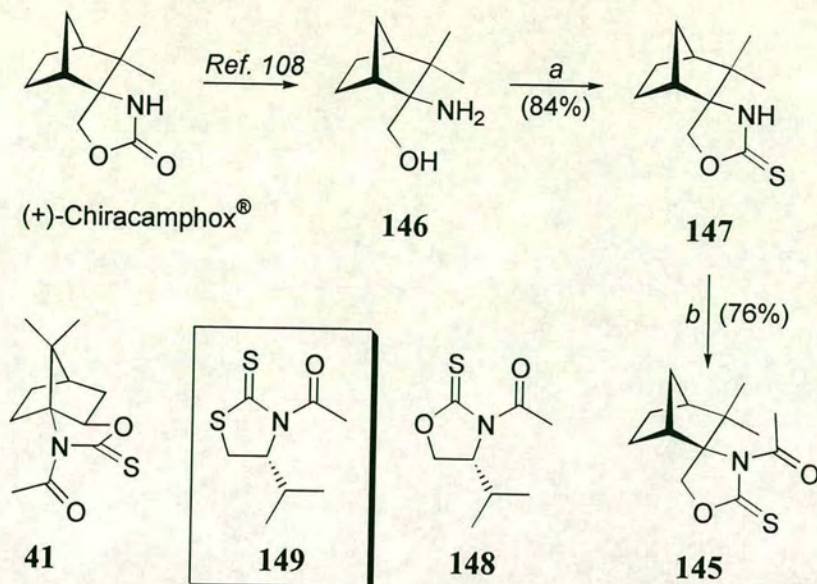
After conducting a series of model studies as discussed in **Chapter 2** and **3** a total synthesis of the natural product octalactin A was undertaken. The attempted route to this natural product will be presented and discussed in the following chapter. Whilst the methodology had been developed for the major steps in the synthesis (*anti* aldol coupling, phosphonate displacement, HWE coupling, deprotection and selective oxidation), it was still necessary to synthesise the two major aldehyde fragments **4** and **5** required for the synthesis.

4.1 SYNTHESIS OF ALDEHYDE 5

The synthesis of the aldehyde required an acetate aldol coupling between a suitable acetate equivalent and isobutyraldehyde.

Whilst a number of methods exist for such a reaction as discussed in **Chapter 1**, there is still a need to develop methodology in this area as the aldol reactions of this type are not as stereoselective or as reliable as their propionate equivalents.

As well as the auxiliaries developed by Nagao⁷³, there have been several camphene based auxiliaries including **41** synthesised by Yan³⁵ for the purpose of this transformation. Most of these exhibit good selectivity in aldol reactions with simple aldehydes, but as mentioned above the selectivity does not rival that of their propionate counterparts. To this end, the acetate auxiliary **145** has been synthesised for use in this transformation (**Scheme 66**) in attempt to improve on current selectivities.



(a) Et₃N, CS₂, THF, reflux, 16 h; (b) i. NaH, THF, 0 °C, 30 min; ii. Acetyl chloride, THF, 0 °C, 30 min.

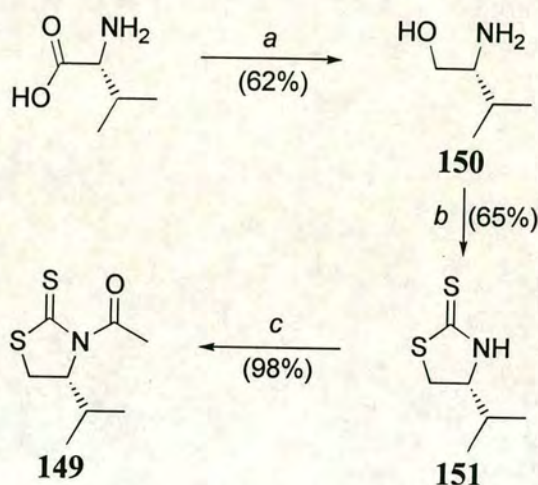
Scheme 66 *Oxazolidinethione and thiazolidinethione acetate equivalents*

Starting from (+)-Chiracamphox^{®107}, the oxazolidinone was hydrolysed to the known amino alcohol¹⁰⁸ **146**, and converted to the oxazolidinethione **147** (CS₂, Et₃N, THF, 16 h, 84%). This, followed by acetylation (acetyl chloride, NaH, THF, 76%), furnished the auxiliary **145**.

As yet no aldol reactions using this auxiliary have been attempted, however, the chemistry of this compound remains of interest to the Hulme group and has the potential to expand the repertoire of acetate aldol auxiliaries available to the organic chemist.

4.1.1 Acetate Aldol Coupling

Due to the relative ease of synthesis and a relatively high degree of selectivity conferred with tin enolates and achiral aldehydes⁷³, valine derived acetate **149** was chosen for the construction of aldehyde **5**. Acetate **149** and the methodology of Yan³⁵ in the use of titanium enolates, were combined in an attempt to give a highly stereoselective transformation in this reaction. The choice of titanium enolate lay in the enhanced stereoselectivity and reliability displayed in the reaction of **149** with a series of α,β -unsaturated aldehydes as compared to the corresponding reactions of the tin enolate.¹⁰⁹

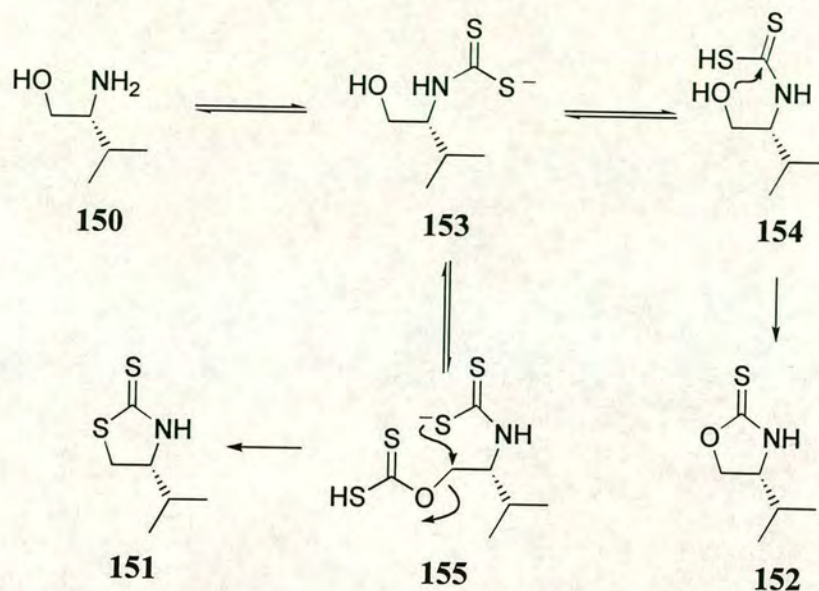


(a) i. NaBH_4 , I_2 , THF, 66°C , 20 h; ii. KOH (20% aq.), rt, 15 h; (b) CS_2 , NaOH (aq.), 100°C , 16 h; (c) i. NaH, THF, 0°C 20 min; ii. acetyl chloride, 0°C , 1 h.

Scheme 67 Synthesis of the thiazolidinethione auxiliary **149**

The auxiliary **149** was synthesised in 3 steps from *R*-valine. Reduction of the amino acid using the I_2/NaBH_4 conditions of Meyers¹¹⁰ afforded *R*-valinol **150** in a respectable 62% yield. Cyclisation of the amino alcohol (CS_2 , 1 *N* NaOH) resulted in a 65% yield of thiazolidinethione **151** (Scheme 67). The lower than expected yield was due to a large amount of unreacted oxazolidinethione **152** (Scheme 58) which can be converted to the thiazolidinethione **151** by further treatment with CS_2/NaOH .

The formation of both of these heterocycles can be explained by consideration of the mechanistic pathway as reported by Le Corre.¹¹¹

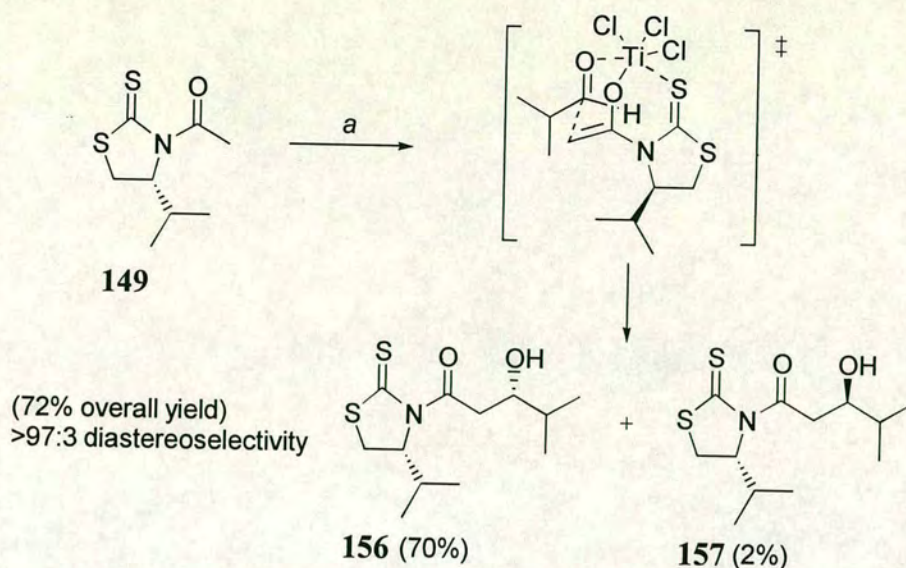


Scheme 68 Mechanism of formation of thiazolidinethione **151** and oxazolidinethione **152**

Under basic conditions (1 N Na_2CO_3 (aq.), 100 °C, 15 min), CS_2 reacts mainly with the amino group giving dithiocarbamate **153**, in equilibrium with **150**. A subsequent nucleophilic attack on the thiocarbonyl affords the oxazolidinethione **152**. However, under more forcing conditions (1 N NaOH (aq.), 100 °C, 16 h), with a vast excess of CS_2 the intermediate **154** can be converted to intermediate **155** which then produces **151** via an intramolecular cyclisation (**Scheme 68**).

Reaction of **151** with NaH /acetyl chloride produced the desired acetylated auxiliary **149** in 93% yield.

The titanium enolate was formed using modified conditions of Yan³⁵ (TiCl_4 , Pr_2EtN , CH_2Cl_2) and the aldol adduct could be attained using two equivalents of isobutyraldehyde as a 97:3 diastereomeric mixture of **156** and **157**. These diastereomeric products could be separated by careful chromatography to give **156** in 70% yield and 2% of the minor diastereomer **157** (**Scheme 69**).

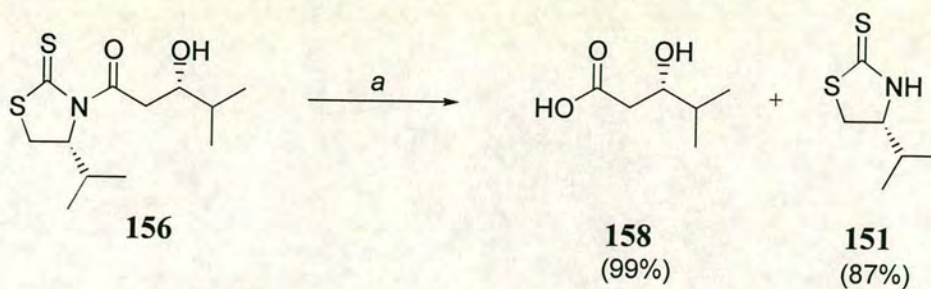


(a) i. TiCl_4 , $^i\text{Pr}_2\text{EtN}$, CH_2Cl_2 , -78°C ; ii. Isobutyraldehyde.

Scheme 69 Titanium-mediated acetate aldol reaction

When a 0.1 M solution of TiCl_4 in CH_2Cl_2 was used instead of neat TiCl_4 a substantial loss of stereoselectivity and a low yield was noted. It was thought that this could be due to an appreciable amount of HCl in the titanium tetrachloride solution, causing cleavage of the acetate group. This was confirmed by the presence of thiazolidinethione **151** in the product mixture in this case.

In order to confirm the absolute stereochemistry of the hydroxyl centre in the major diastereomer, the aldol adduct **156** was subjected to hydrolysis using lithium hydroperoxide (LiOH , H_2O_2 , THF) and converted to the known β -hydroxy acid **158** (Scheme 70) in almost quantitative yield.³⁵



(a) LiOH, H₂O₂, THF, rt, 0 °C.

Scheme 70 LiOH promoted hydrolysis

The stereochemistry of the acid was confirmed by comparison of the optical rotation with that of the literature compound, and the auxiliary **151** was recovered intact in 87% yield.

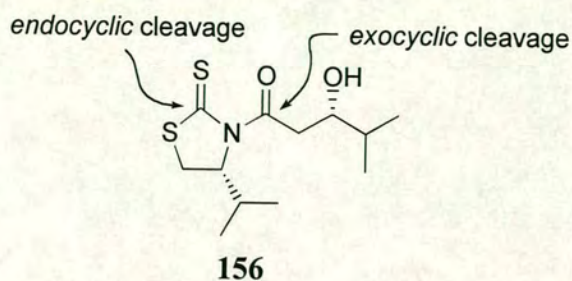
4.1.2 Auxiliary cleavage

It was thought that a *p*-methoxybenzyl (PMB) moiety as a protecting group on the free hydroxyl in the aldol adduct **156** would allow for a facile and mild oxidative deprotection step in the latter stages of the synthesis. The original strategy involved a PMB protection of the free hydroxyl followed by a low temperature DIBAL reduction to the desired aldehyde **5**.

Initial studies into the protection involved the use of PMB trichloroacetimidate and a catalytic amount of triflic acid (TfOH).¹¹² A low yield and a complex mixture of products precluded any further investigation into this approach. Therefore, a more robust and reliable synthesis was then sought.

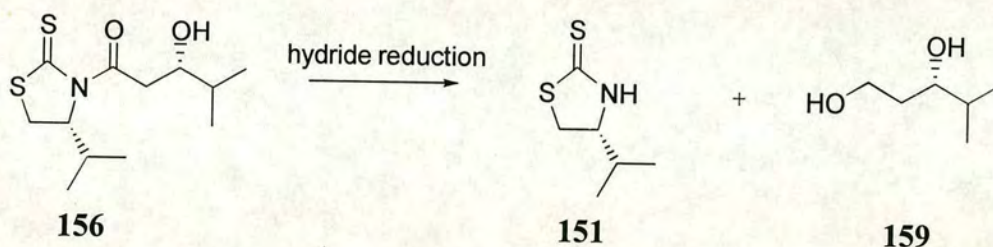
The thiazolidinethione auxiliaries have a further advantage over the related oxazolidinones in that they do not require strong hydride reagents such as LiAlH₄, or DIBAL, to effect the reduction to the free auxiliary and a resultant alcohol. Whilst these reagents were originally used to reduce aldol adduct **156** to the corresponding 1,3-diol **159**, it was found that there was a significant amount of competing *endo* cleavage rather than the desired *exo* cleavage (Scheme 71) of the thiazolidinethione

causing difficult separation of the diol and lowering yields of both **159** and the recovered auxiliary **151**.



Scheme 71 *Endocyclic versus exocyclic cleavage*

It was found that using the conditions for the reduction of oxazolidinethione derived aldol adducts described by Nagao⁷³ (NaBH_4 , THF (aq.), rt) the aldol adduct **156** could be easily reduced to the desired diol **159**. The results of the three reduction methods are summarised in **Table 5**.



Entry	Conditions	Yield	
		151	159
1	LiAlH_4 , Et_2O , $-78\text{ }^\circ\text{C}$ to $0\text{ }^\circ\text{C}$	55%	59%
2	DIBAL (1.0 M solution in toluene), CH_2Cl_2 , $-78\text{ }^\circ\text{C}$, 10 min	61%	42%
3	NaBH_4 , THF (aq.), rt, 30 min	88%	85%

Table 5 *Hydride reduction of the aldol adduct*

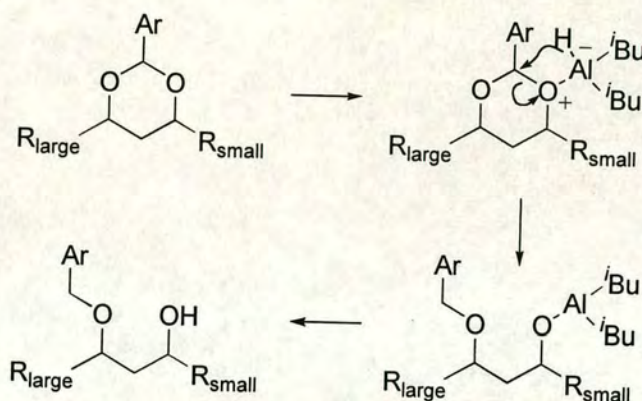
Reduction of the aldol adduct with sodium borohydride as well as being the optimum method, also allowed for the easy monitoring of the reaction. The reaction

was followed to completion by the disappearance of the brightly yellow coloured aldol adduct **156**.

4.1.3 PMB protection

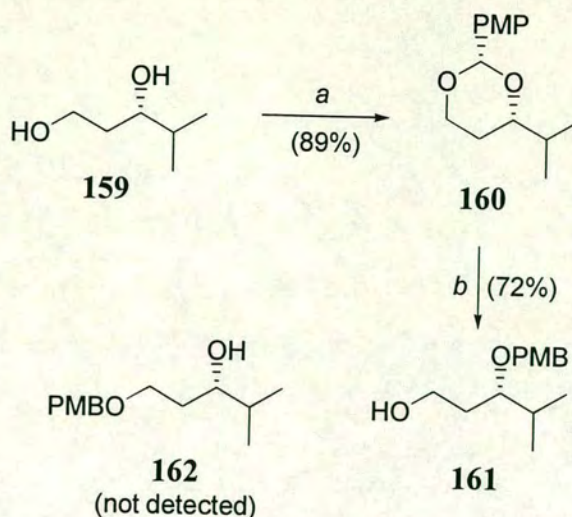
It is possible to selectively protect a 1,2- or a 1,3-diol at the secondary hydroxyl with a PMB or benzyl group *via* its 1,2- or 1,3-diol acetal.¹¹³

Using an excess of DIBAL, Takano¹¹⁴ reduced a number of benzylidene acetals to the corresponding benzyl mono protected diols. Although the cleavage is presumed to occur through internal delivery of hydride, an external pathway is also possible as more than two equivalents of DIBAL are required to give satisfactory yields (**Scheme 72**).



Scheme 72 Mechanism of DIBAL reduction

Initial attempts to form the acetal using *p*-methoxybenzaldehyde and *p*-toluenesulfonic acid resulted in poor yields of the desired product and incomplete conversion. Using standard conditions (TsOH.H₂O, *p*-methoxybenzaldehyde dimethyl acetal, DMF, rt), the diol **159** was converted to the acetal **160** (89%) as a single diastereomer. The intermediate **160** was then reduced to the monoprotected diol **161** using the conditions of Takano¹¹⁴, with an excess of DIBAL in 72% yield (**Scheme 73**).



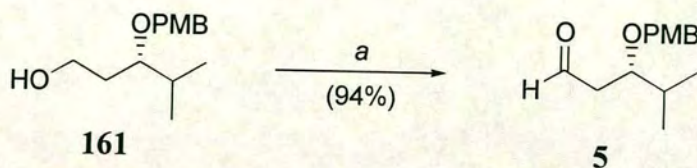
(a) TsOH.H₂O, *p*-methoxybenzaldehyde dimethyl acetal, DMF, rt, 10 h; (b) DIBAL (1.0 M solution in toluene), CH₂Cl₂, 0 °C.

Scheme 73 Selective PMB protection of the secondary hydroxyl

The primary protected alcohol **162** resulting from unselective reduction of the acetal **160** was not observed.

4.1.4 Oxidation

A number of mild methods exist for the formation of aldehydes from primary alcohols,^{77,78,95} but as the oxidation of the primary alcohols **80-82** with IBX had proceeded very smoothly, it was decided to use the conditions previously developed for the oxidation.



(a) IBX, DMSO/THF, rt, 1 h.

Scheme 74 Oxidation to aldehyde **5**

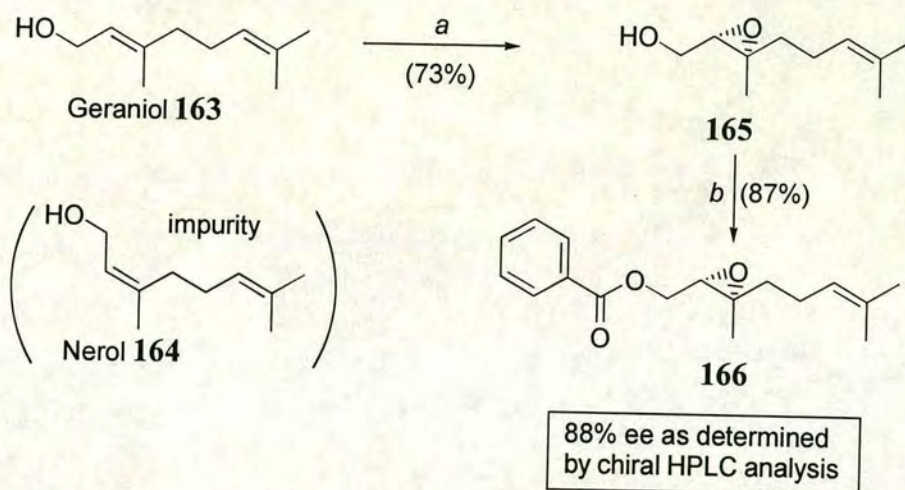
Oxidation of the alcohol **161** gave the desired aldehyde **5** in an excellent 94% yield (**Scheme 74**). Despite this synthetic route being longer (5 steps from acetate **149**) compared to the original route, the synthesis shown above offers a robust and reliable synthesis of the desired aldehyde **5**.

4.2 SYNTHESIS OF ALDEHYDE 4

4.2.1 Epoxidation

The use of the Sharpless asymmetric epoxidation has found use in countless approaches to natural product synthesis since its introduction in 1980.¹¹⁵ The catalytic version of the reaction was published in 1987 and is now widespread in its use in the laboratory and on an industrial scale.¹¹⁶

The synthesis of aldehyde **4** began with epoxidation of the cheap and readily available allylic alcohol, geraniol **163**. Whilst Sharpless found it possible to produce the desired epoxide in 91% enantiomeric excess (ee), initial attempts at the epoxidation of geraniol produced material of very low enantiomeric excess.



- (a) *L*-(+)-DET, Ti(O^{*i*}Pr)₄, ^{*t*}BuOOH, 4 Å mol. sieves, CH₂Cl₂, -25 °C, 1.5 h;
 (b) Benzoyl chloride, Et₃N, CH₂Cl₂, 0 °C, 40 min.

Scheme 75 Sharpless epoxidation of geraniol

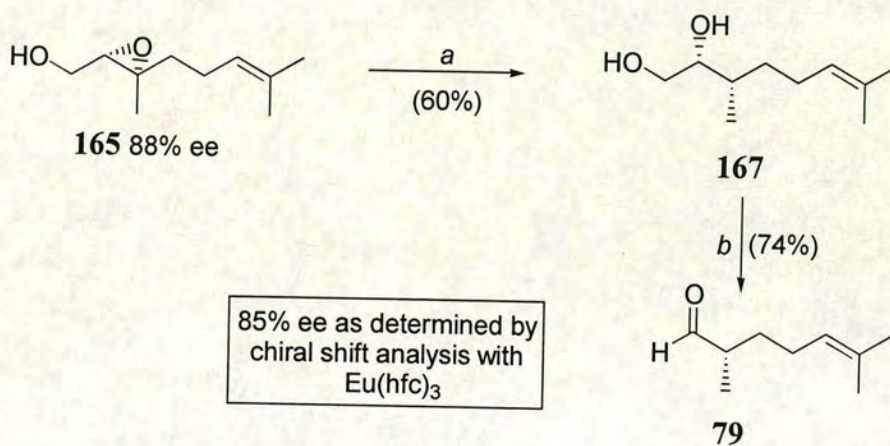
However, after rigorous drying of all of the reagents prior to use and treatment of the ^{*t*}butyl hydroperoxide with several batches of 4 Å molecular sieves immediately prior to use, it was possible to obtain the desired epoxide **165** in 88% ee consistently and with a good yield (73%) after kugelrohr distillation (**Scheme 74**).

The epoxide was found to contain an impurity of *c.* 2-5% resulting from epoxidation of nerol **164**, and as the geraniol purchased from Acros was reported as being 99.9% pure, it was originally thought that the impurity had arisen from the

epoxidation reaction. However, on examination of the ^1H NMR of the starting material it was found to contain the same amounts of the impurity nerol **164**.⁹

The enantiomeric excess of the epoxide **165** was confirmed by conversion to the benzoate ester **166** (Benzoyl chloride, Et_3N , CH_2Cl_2 , $0\text{ }^\circ\text{C}$) and analysis by HPLC on a chiracel OD column (Scheme 75).[†] Care was taken to combine all of the benzoate ester fractions after chromatography to obtain an accurate value for the enantiomeric excess of the epoxide.[‡]

4.2.2 1,2-Diol Formation and Periodate Cleavage



(a) NaBH_3CN , $\text{BF}_3\cdot\text{OEt}_2$, THF, rt; (b) NaIO_4 , pH 7 buffer, CH_2Cl_2 , rt.

Scheme 76 1,2-Diol formation and periodate cleavage

Several reagent combinations exist for the opening of epoxides at the more sterically hindered end.¹¹⁸

⁹ The impurity was confirmed as nerol by Acros Chemical Company after GC analysis of the batch and comparison with a known sample of nerol.

[†] The benzoate ester **166** was analysed in comparison to the benzoate ester of the 2*R*,3*R* enantiomer of epoxygeraniol (86% ee prepared by the same method from geraniol using *D*-(-)-diethyl tartrate).

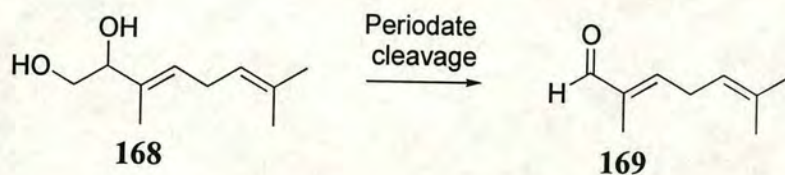
[‡] In an early attempt at the epoxidation, material of 82% ee was obtained. However, after conversion to the benzoate ester and subsequent purification, the individual fractions from the column were analysed by chiral HPLC and a small but significant (*c.* 5%) non linear effect was observed. The early fractions from the column had a lower enantiomeric excess (77-78% ee) than those collected a few fractions later (83-84% ee).¹¹⁷

Of these Taber found $\text{NaBH}_3\text{CN}/\text{BF}_3\cdot\text{OEt}_2$ to be the cleanest and most reliable method. Using these conditions, the epoxide **165** was reduced, resulting in the selective formation of the 1,2-diol **167** (60% yield) and with no evidence for any 1,3-diol (**Scheme 76**).

Periodate cleavage of the 1,2-diol **167**, using the mild conditions of Chamberlain¹¹⁹ (NaIO_4 , pH 7 buffer, CH_2Cl_2) gave the desired α -methyl aldehyde **79** (74% yield^y). The enantiomeric excess of the aldehyde was determined as being 85% through ^1H NMR chiral shift studies at 200 MHz using $\text{Eu}(\text{hfc})_3$. This reduction of the enantiomeric excess (88% in the epoxide **165**) was attributed to the impurity nerol **164** in the starting geraniol.^z

On one occasion the formation of a small amount of a previously unseen impurity was observed and identified as the α,β -unsaturated aldehyde **169**.

Whilst it was unclear where this impurity had come from, it was thought to have arisen from the periodate cleavage of the diol **168**, a small amount of which must have been formed in and carried through from the reductive opening of the epoxide (**Scheme 77**).



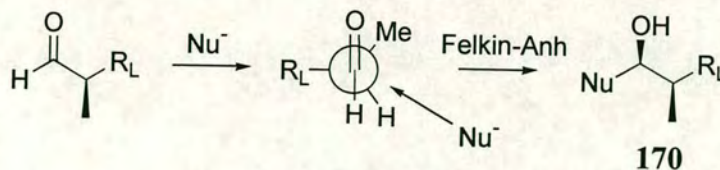
Scheme 77 Periodate cleavage and formation of α,β -unsaturated aldehyde **169**

^y As the reaction was observed to go to completion, (as judged by tlc analysis), the moderate yield was attributed to the volatility of the aldehyde **79**.

^z Epoxidation of nerol **164**, followed by opening to the 1,2-diol (2,3-*anti* relationship) and periodate cleavage would result the formation of *ent*-**79** and thereby reduce the enantiomeric excess. [As it was thought that the Lewis acidity of the shift reagent might cause unwanted epimerisation of the aldehyde, the aldehyde **79** was swiftly reduced to corresponding primary alcohol using sodium borohydride and converted to the benzoate ester for chiral HPLC analysis. The two enantiomers however, co-ran under a variety of conditions.]

4.2.3 Acetate Aldol Approach to the C(3)-C(4) Bond Formation

The Felkin-Anh model for nucleophilic attack on an α -chiral aldehyde predicts the formation of **170** where R_L is the largest group on the α -chiral centre (Scheme 77).^{120,121}

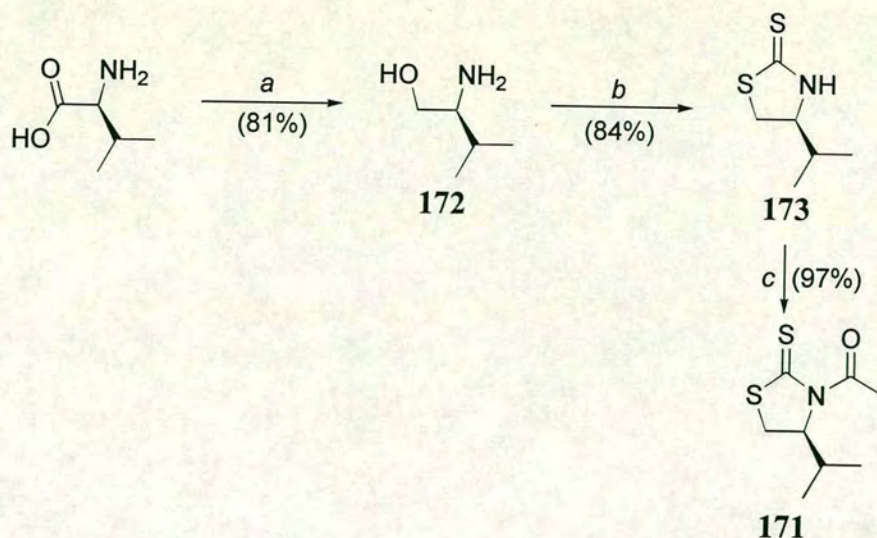


Scheme 78 Felkin-Anh model for nucleophilic attack on α -chiral aldehydes

When a reaction goes through an acyclic transition state, the Felkin-Anh model generally holds. However, aldol reactions which go through a highly ordered transition state have other factors which influence the selectivity.

It is possible to exert a high degree of selectivity from the aldol reactions of methyl ketone equivalents with aldehydes bearing bulky substituents at the α -centre.²² However, the asymmetric induction from an α -methyl group alone in reaction with a methyl ketone or acetate equivalent has been shown to be virtually negligible.²² Therefore, to allow for a stereoselective aldol reaction with aldehyde **79**, all the stereocontrol would have to come from an external source *e.g.* auxiliary control.

Using the conditions as described above for *R*-valine the auxiliary **171** was synthesised in 3 steps from *S*-valine (65% overall yield).

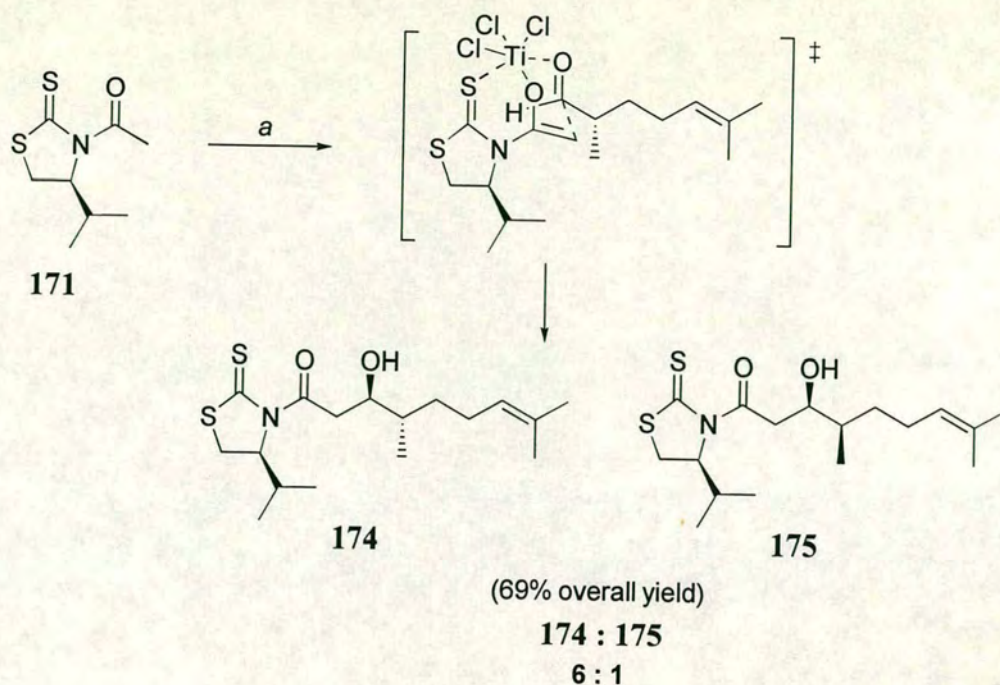


(a) i. NaBH_4 , I_2 , THF, 66°C , 20 h; KOH (20% aq.), rt, 15 h; (b) CS_2 , NaOH (aq.), 100°C , 16 h; (c) i. NaH, THF, 0°C , 20 min; ii. Acetyl chloride, 0°C , 1h.

Scheme 79 *Synthesis of thiazolidinethione auxiliary 171*

The methodology developed for the aldol reaction with isobutyraldehyde in the synthesis of aldehyde **5** was transferred in attempt to give a stereoselective reaction between the acetate equivalent **171** and the α -methyl aldehyde **79**.

Thus, enolisation of **171** under the previously described conditions ($i\text{-Pr}_2\text{EtN}$, TiCl_4 , CH_2Cl_2) and subsequent reaction with **79** (85% ee) produced a 69% yield of the aldol adduct. However, analysis of the crude ^1H NMR showed the product to contain a 6:1 mixture of diastereomers which proved impossible to separate by column chromatography, or by preparative HPLC (Scheme 80).

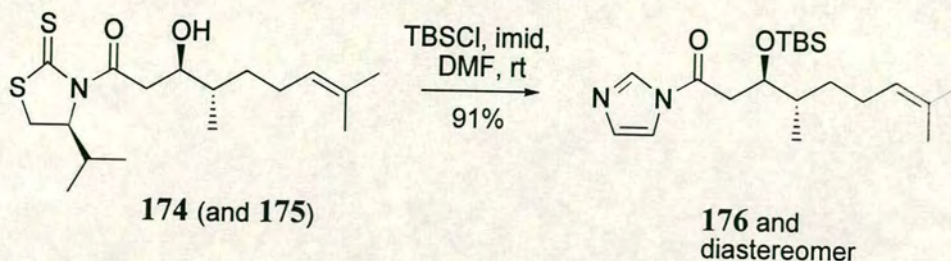


(a) i. TiCl_4 , Pr_2EtN , CH_2Cl_2 , -78°C ; ii. Aldehyde **79**.

Scheme 80 Acetate aldol with α -methyl aldehyde **79**

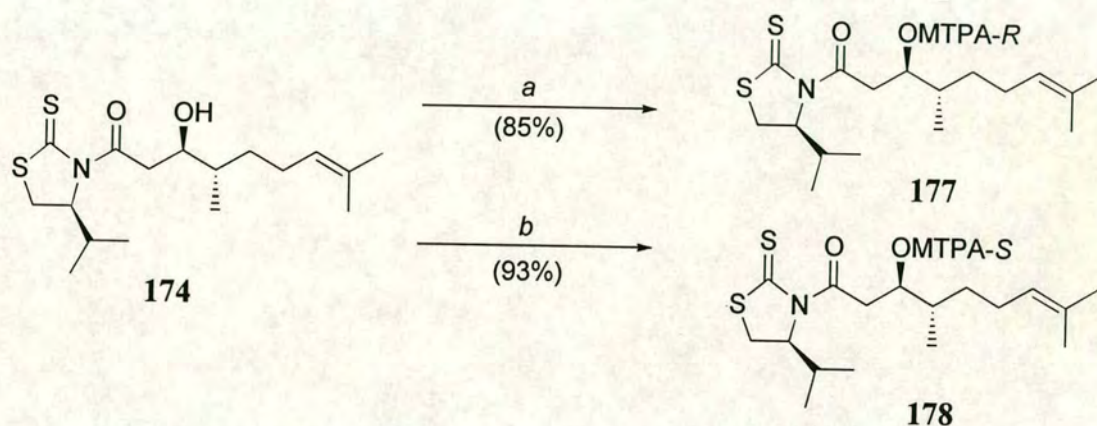
The major diastereomer was confirmed as the expected **174**, by conversion to the Mosher's esters as discussed below, whilst the minor diastereomer was tentatively assigned as aldol adduct **175**.⁹

⁹ In attempt to silylate the free hydroxyl and produce a separable mixture of aldol adducts, the aldol adduct was treated with imidazole and TBSCl. However the expected product was not observed and the sole product isolated was the imidazole **176**.



Assuming no diastereofacial preference from the aldehyde, the maximum possible amount of **175** that can be produced is 7.5%. It would seem therefore, that a substantial degree of epimerisation (*c.* 10%) at the α centre in the aldehyde is occurring prior to aldolisation.

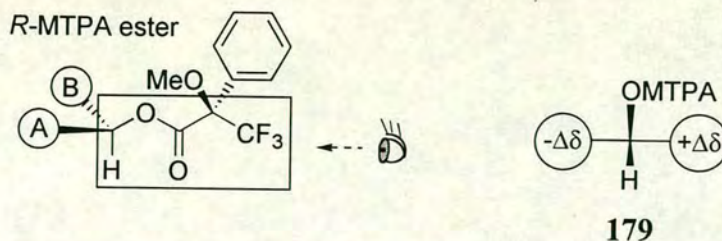
The absolute configuration of the hydroxyl centre (in the major diastereomer) was confirmed by conversion of the aldol adduct to the *R*- and *S*-MTPA (α -methoxy- α -(trifluoromethyl) phenylacetic acid) Mosher's esters **177** and **178** respectively (Scheme 81).¹²²



(a) *R*-MTPA, DCC, DMAP (cat.), CH₂Cl₂, rt, 2 h;
 (b) *S*-MTPA, DCC, DMAP (cat.), CH₂Cl₂, rt, 2 h.

Scheme 81 Mosher's ester synthesis

The method works as follows: 1) Assign as many proton signals as possible of the *R*- and *S*-MTPA esters. 2) Obtain $\Delta\delta$ values ($\Delta\delta = \delta_S - \delta_R$) for the assignable protons. 3) Put the protons with a negative $\Delta\delta$ value on the left hand side of **179** and those with a positive value on the right. 4) Construct a molecular model of the compound in question and confirm that all of the assigned protons are found on the 'correct' sides of the MTPA plane.¹²³



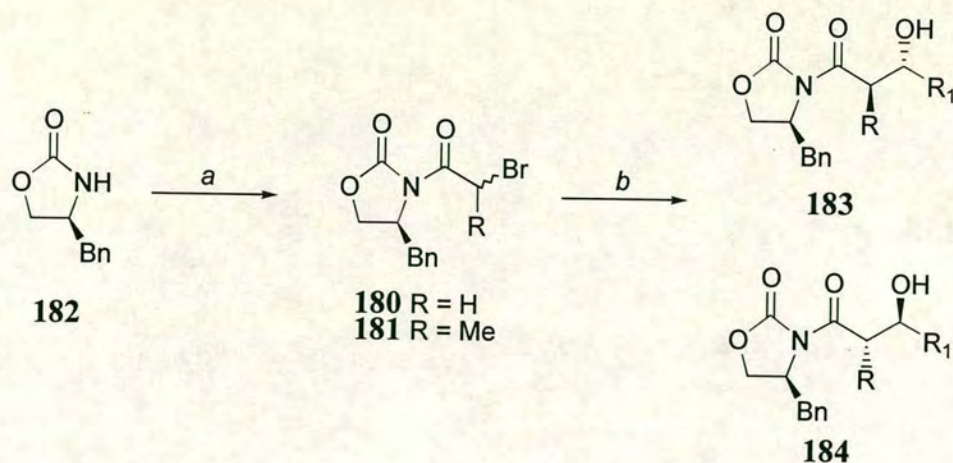
Scheme 82 Model for absolute stereochemical assignment

The absolute values of $\Delta\delta$ must be proportional to the distance from the MTPA moiety. When all of the above conditions have been satisfied, the model 179 will indicate the absolute configuration of the molecule (**Scheme 82**).

Careful analysis of the corresponding ^1H spectra as described by Kakisawa¹²³ confirmed the absolute configuration of the hydroxyl centre as *R*.

4.2.4 The Asymmetric (Cr-Mediated) Reformatsky Reaction

As discussed in **Chapter 1**, there are a number of advantages of the Reformatsky reaction which include the formation of the enolate at a predetermined site, under neutral conditions and in the presence of a variety of functional groups. However, there are only a few examples of asymmetric syntheses with Reformatsky type reagents. Until the recent report by Wessjohann¹²⁴, the enantiomeric and diastereomeric selectivity of this reaction were limited. Wessjohann showed, by use of the bromo acetyl oxazolidinones **180** and **181** (synthesised from the oxazolidinone **182**) developed by Evans, that it is possible to exert an excellent degree of diastereoselectivity in the chromium mediated Reformatsky reaction with a series of unfunctionalised aldehydes. These results are summarised in **Table 6**.



(a) i. $n\text{-BuLi}$, THF, $-78\text{ }^{\circ}\text{C}$; ii. Bromoacetyl bromide, THF, $-78\text{ }^{\circ}\text{C}$; (b) R^1CHO , CrCl_2 , LiI , THF, $20\text{ }^{\circ}\text{C}$.

Entry	R	R ₁	Yield ^a	<i>anti:syn</i>	d.r. 183:184
1	Me	ⁱ Pr	83%	>95:5	>98:2
2	Me	Ph	76%	89:11	97:3
3	H	ⁱ Pr	88%	-	>96:4
4	H	Ph	85%	-	87:13

(a) Combined yield of all diastereomers **183** and **184**

Table 6 Chromium-Reformatsky reaction

The reaction gave excellent *anti:syn* selectivity with the *anti* stereochemistry in **183** favoured over that in **184**.

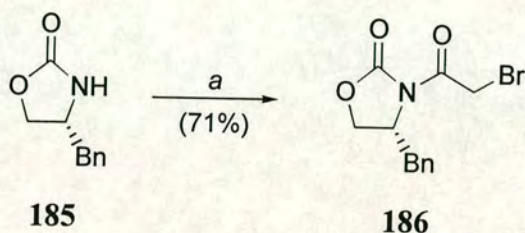
More interestingly, the reaction also gave good yields for the reaction of aldehydes with the α unsubstituted bromoacetyl auxiliary **180** to give the adduct **183** with much greater selectivity than that observed for the corresponding lithium and boron enolates (52:48 dr).³³

Of particular interest was the reaction of bromoacetyl oxazolidinone **180** with isobutyraldehyde in its chromium mediated Reformatsky reaction giving almost exclusive formation of the α unsubstituted aldol product **183** (R = H) (Table 6, entry 3). The excellent selectivity in the reaction as well as the possibility of converting the

oxazolidinone **182** in a one pot reaction¹²⁵ to the aldol adduct **183**, encouraged the possible use of this reaction in the construction of the C(3)-C(4) bond in octalactin A.

4.2.5 Reformatsky Approach to the C(3)-C(4) Bond Formation

The acylated auxiliary **186** was synthesised from the oxazolidinone **185** by the conditions of Evans¹²⁶ (*n*BuLi, bromoacetyl bromide, THF, -78 °C) and isolated as a crystalline solid after recrystallisation from ether (Scheme 83).^Φ



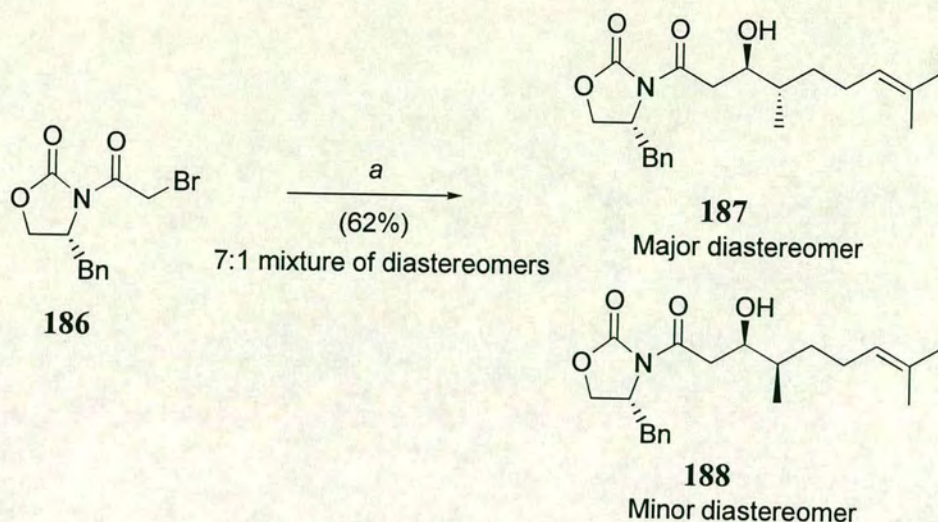
(a) i. *n*BuLi, THF, -78 °C; ii. Bromoacetyl bromide, THF, -78 °C, 20 min.

Scheme 83 Synthesis of the bromoacetyl auxiliary **186**

As suggested by Wessjohann the chromium (II) chloride and lithium iodide used for the reaction were of the upmost purity and the reaction was conducted under strictly anhydrous conditions.

Reformatsky reaction of bromoacetyl oxazolidinone **186** with aldehyde **79** (Cr(II)Cl₂, LiI, THF, rt) gave a respectable yield (62%) of the aldol product as a 7:1 mixture of diastereomers (Scheme 84).

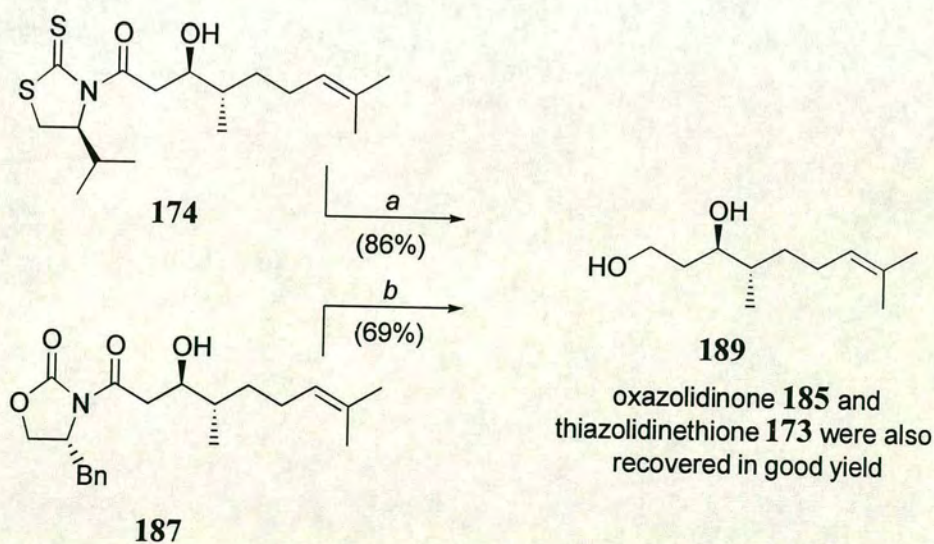
^Φ Whilst being stable for a few days in the freezer, the oxazolidinone slowly decomposed and was generally used within a day of its synthesis.



(a) **79**, CrCl_2 , LiI , THF, rt, 3h.

Scheme 84 Asymmetric chromium-mediated Reformatsky reaction

Unfortunately, it proved impossible to separate the diastereomers through column chromatography or by preparative HPLC (reverse and normal phase) under a variety of conditions.



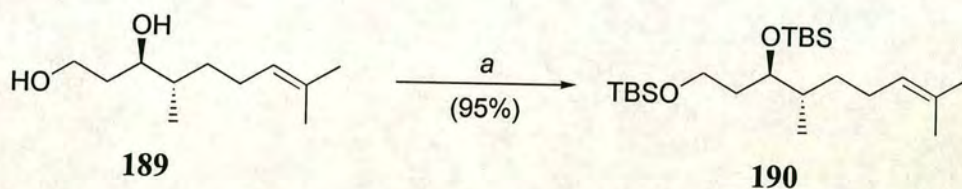
(a) NaBH_4 , THF, rt; (b) LiBH_4 , THF, rt, 2.5 h.

Scheme 85 Hydride reduction of aldol adducts **174** and **187**

The stereochemistry of the major product was confirmed by reduction to the 1,3-diol **189** (LiBH_4 , THF, rt, 2.5 h, 69%) and comparison of the ^1H and ^{13}C NMR spectra of the diol formed by reduction of the thiazolidinethione aldol adduct **174** (NaBH_4 , THF, rt, 86%) (Scheme 85).

Whilst the major diastereomer was confirmed as **187**, insufficient spectroscopic data was available to fully assign the minor product in this reaction. It was therefore surmised (as only 2 diastereomers are observed in the reaction) that the minor diastereomer is **188** assuming no diastereofacial preference for the aldehyde. The formation of **188** is a result of the stereoselective Reformatsky reaction with further epimerised (*c.* 7%) aldehyde **79**. Further investigations using previously epimerised aldehyde (derived from thermodynamic equilibration at the α centre) would help to confirm this hypothesis, but were not conducted due to time constraints.

The primary and secondary hydroxyls of the diol **189** were protected as their TBS ethers (TBSOTf, 2,6-lutidine, CH_2Cl_2 , 0 °C, 30 min, 95%) to give **190**.[§] (Scheme 86).



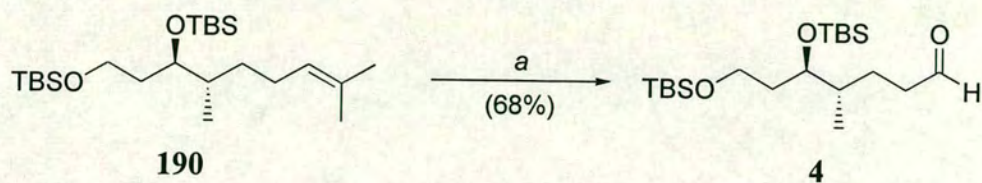
(a) TBSOTf, 2,6-lutidine, CH_2Cl_2 , 0 °C, 1.5 h.

Scheme 86 Di-TBS protection of the 1,3-diol **189**

[§] A previous attempt at selectively protecting the secondary hydroxyl as its PMB ether and the primary hydroxyl as its TBS ether gave a complex mixture of products after ozonolysis.

4.2.6 Ozonolysis

The transformation to the desired aldehyde required an oxidative cleavage of the double bond. Treatment of **190** under ozonolysis conditions gave a good yield of the desired aldehyde **4** (Scheme 87).¹¹⁹



- (a) i. O₃, Sudan III indicator, pyridine, CH₂Cl₂/MeOH, -78 °C, 20 min;
 ii. DMS, -78 °C to rt.

Scheme 87 Ozonolytic cleavage of **190**

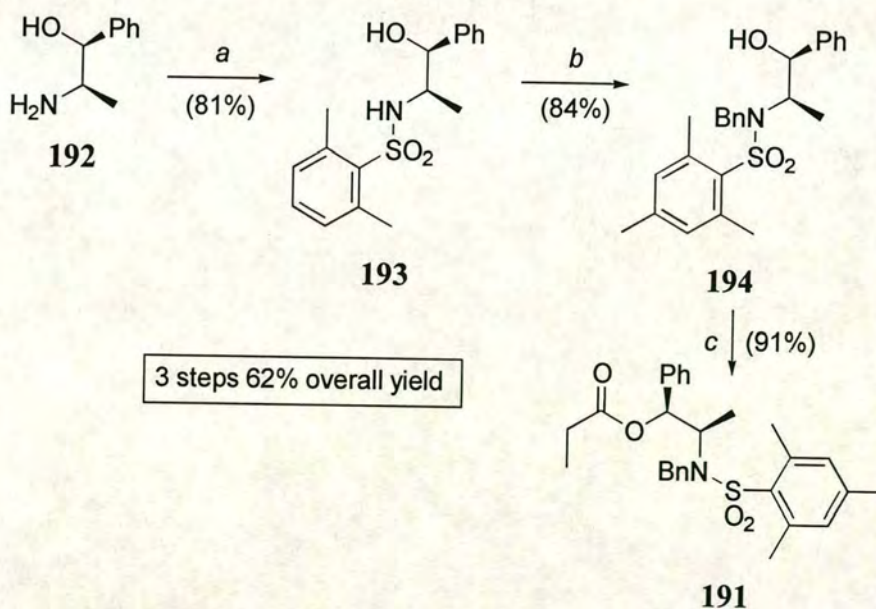
The synthesis, as discussed above, offers an efficient 7 step synthesis of aldehyde **4** from the cheap and readily available geraniol.

4.3 ANTI ALDOL APPROACH TO THE C(7)-C(8) BOND FORMATION

The use of the 'butyl thioester **88** proved a suitable propionate equivalent and gave excellent *anti:syn* selectivities in its aldol reaction with simple aldehydes as discussed in **Chapter 2**. However, the practical difficulties associated with the synthesis of the chiral bromoborane required for an asymmetric version of the reaction prompted the search for a more reliable alternative. As discussed in **Chapter 1** there exist a number of possible methods for the generation of *anti* aldol adducts in a stereoselective manner.

Also discussed in **Chapter 1** was the development by Masamune²⁷ of the norephedrine derived auxiliary **191** for the efficient, reliable stereoselective construction of *anti* aldol adducts. Its utility in synthesis was also also demonstrated.²⁸ The ready availability of the auxiliary, combined with the mildness of the boron aldol reaction and the ease of operation warranted its use in the C(7)-C(8) bond construction of octalactin A.

4.2.1 Auxiliary Synthesis



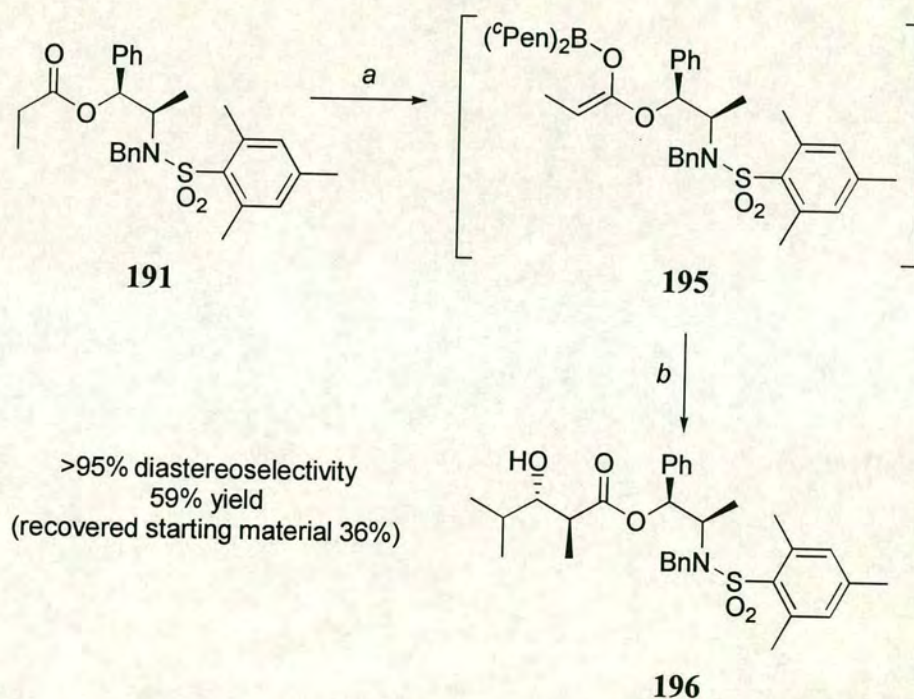
(a) MesSO₂Cl, Et₃N, CH₂Cl₂, 0 °C, 2 h; (b) i. 'BuOK, DMF, 0 °C, 30 min; BnBr, rt, 4.5 h; (c) Propionyl chloride, pyridine, 0 °C to room temperature, 18 h.

Scheme 88 Masamune's auxiliary synthesis

The auxiliary **191** was synthesised using the conditions of Masamune in 3 steps (62% overall yield). Selective sulfonylation of the amino group to give **193** followed by selective *N*-benzylation (**193**→**194**) and acylation gave the desired propionate derivative **191** (Scheme 88).

4.3.2 *Anti* Aldol Coupling

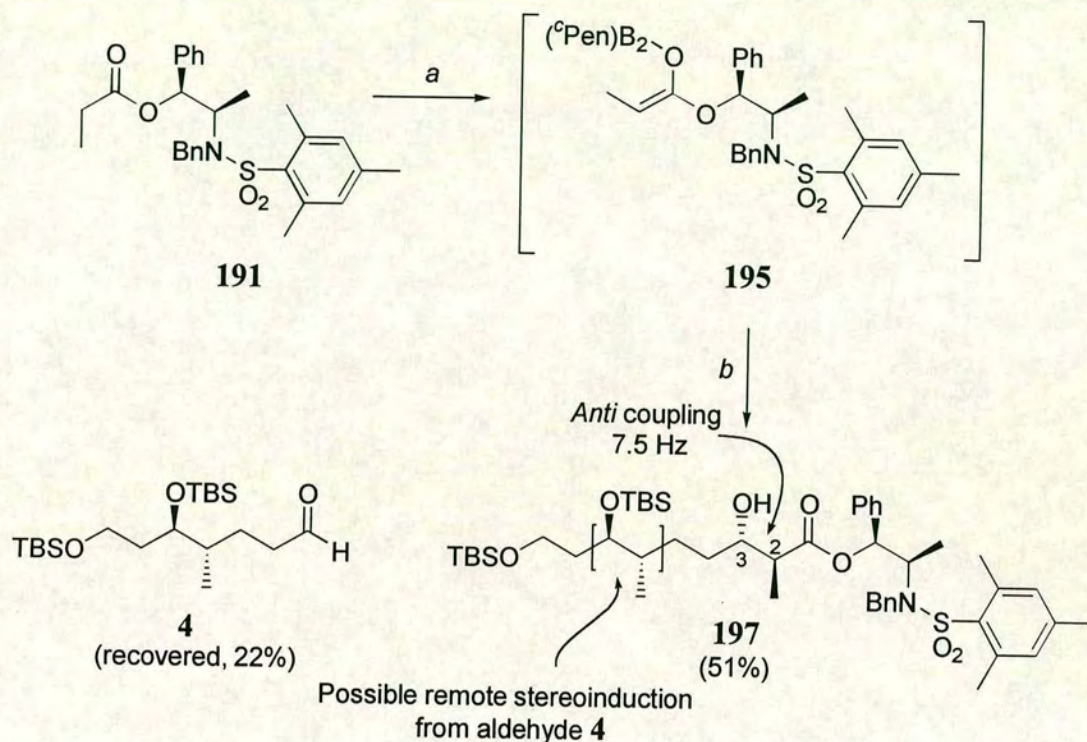
The *anti* aldol reaction of **191** with isobutyraldehyde was repeated using commercially available dicyclopentylboron triflate and diisopropylethylamine to give a comparable yield of **196** (95% based on recovered starting material) to that observed by Masamune, as a single diastereomer ($\geq 95:5$ *anti:syn* and $\geq 95:5$ diastereofacial selectivity for the *anti* diastereomer) (Scheme 89).



Scheme 89 *Anti* aldol reaction with isobutyraldehyde

Encouraged by the high selectivity of the reaction with isobutyraldehyde the reaction was attempted with the complex aldehyde **4**. Enolisation, under the same

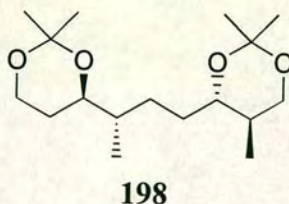
conditions as above, using an excess of enolate (2.5 eq.), gave a moderate yield (51%) of the desired *anti* aldol adduct **197** as a hygroscopic foam (starting material recovered, 22%) (Scheme 90).



(a) $t\text{Pr}_2\text{EtN}$, $(^c\text{Pen})_2\text{BOTf}$, CH_2Cl_2 , -78°C , 2 h; (b) Aldehyde **4**, -78°C , 1.5 h then 0°C for 1.5 h.

Scheme 90 *Anti aldol reaction with aldehyde 4*

Analysis of the 600 MHz ^1H NMR showed the product to be a 6:1 mixture of diastereomers which were inseparable by chromatography. Attempts to confirm the relative (*anti*) stereochemistry of the major diastereomer by converting the aldol adduct to the 1,3-diol acetonide (LiBH_4 reduction followed by acid catalysed acetonide formation) failed.



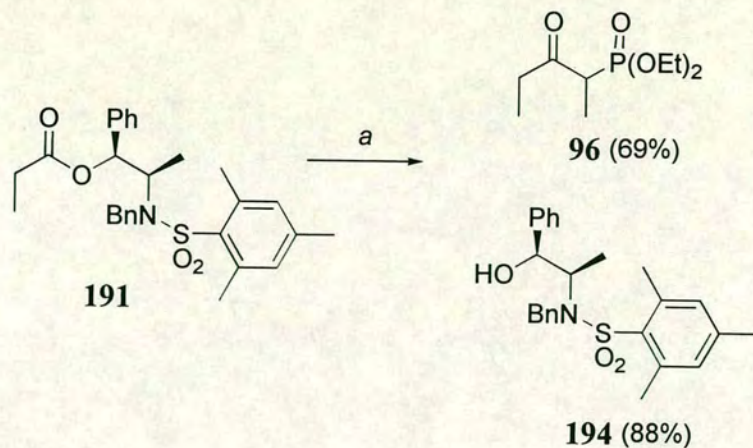
Scheme 91 *Bis-acetonide resulting from desilylation and acetonide formation*

The impure isolated material was found to be mainly the product of cleavage of the two TBS groups and the reaction of the free hydroxyls to give the *bis*-acetonide **198** (Scheme 91), this combined with the inseparable impurities made it impossible to assign the relevant signals and couplings.

The stereochemistry of the major diastereomer was thus assigned on the basis of a large (7.5 Hz) *anti* coupling between the C(2) and C(3) protons in **197** and the diastereofacial selectivity was assumed on the basis of precedent.^{27,28} The stereochemistry of the minor diastereomer was not confirmed. It is unclear as to the relative stereochemistry of the minor product and whether or not there is any remote stereoiduction being conferred by the aldehyde.

4.3.3 Anionic Displacement

The anionic displacement conditions developed for the thioester derivatives as discussed in Chapter 2 and 3 were applied to auxiliary **191**. Addition of the anion derived from diethyl ethanephosphonate to **191** gave a good yield of the simple phosphonate **96** (see Section 2.4.1) with concomitant recovery of the free auxiliary **194** (88% yield) (Scheme 92).

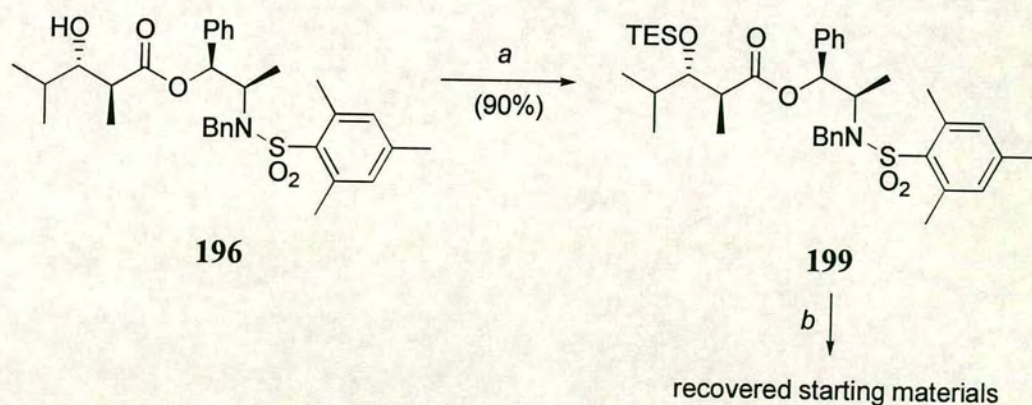


(a) i. n BuLi, diethyl ethanephosphonate THF, -78°C , 45 min; ii. add to ester **191**, -78°C , 20 min.

Scheme 92 Anionic displacement of ester **191**

Whilst it is possible that a certain degree of facial selectivity may have been exerted by the auxiliary in the displacement, no attempts were made to assess the enantiomeric excess of, or sense of stereochemical induction in the phosphonate **196**.

The aldol adduct **196** was protected as its triethylsilyl (TES) ether (TESCl, imidazole, DMF, rt, 90%) to give protected aldol adduct **199** and treated with the anion of diethyl ethanephosphonate (Scheme 93).

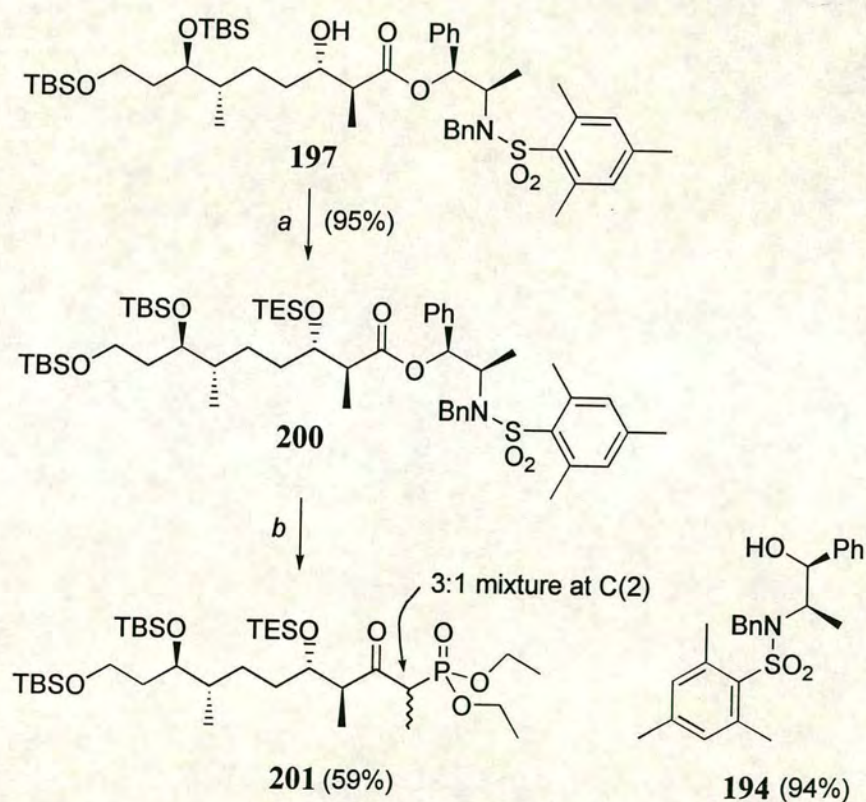


(a) TESCl, imidazole, DMF, rt, 18h; (b) i. n BuLi, diethyl ethanephosphonate THF, -78°C , 45 min; ii. add to ester **199**, -78°C , 20 min; iii. NH_4Cl (sat. aq.) at -78°C .

Scheme 93 TES protection and anionic displacement

The reaction appeared to have gone to completion by the disappearance of the starting material and the formation of two low R_f spots, one of which corresponded to that of the free auxiliary **194**. However, on quenching of the reaction at $-78\text{ }^{\circ}\text{C}$ only starting materials were obtained, suggesting that the reaction may have occurred during the tlc sampling process *i.e.* as the material warmed to $>-78\text{ }^{\circ}\text{C}$.

The aldol adduct **197** was protected as its triethylsilyl (TES) ether (TESOTf, 2,6-lutidine, CH_2Cl_2 , $0\text{ }^{\circ}\text{C}$, 90%) giving **200**. Reaction of the protected aldol adduct **200** under the conditions described above, with the additional measure of slowly warming to $0\text{ }^{\circ}\text{C}$ before quenching the reaction, gave a 59 % yield of **201** as a 3:1 mixture of diastereomers at C(2) (Scheme 94).



(a) TESOTf, 2,6-lutidine, CH_2Cl_2 , $0\text{ }^{\circ}\text{C}$, 30 min; (b) i. $n\text{-BuLi}$, diethyl ethanephosphonate THF, $-78\text{ }^{\circ}\text{C}$, 45 min; ii. add to ester **200**, $-78\text{ }^{\circ}\text{C}$, 20 min followed by 10 min at $0\text{ }^{\circ}\text{C}$.

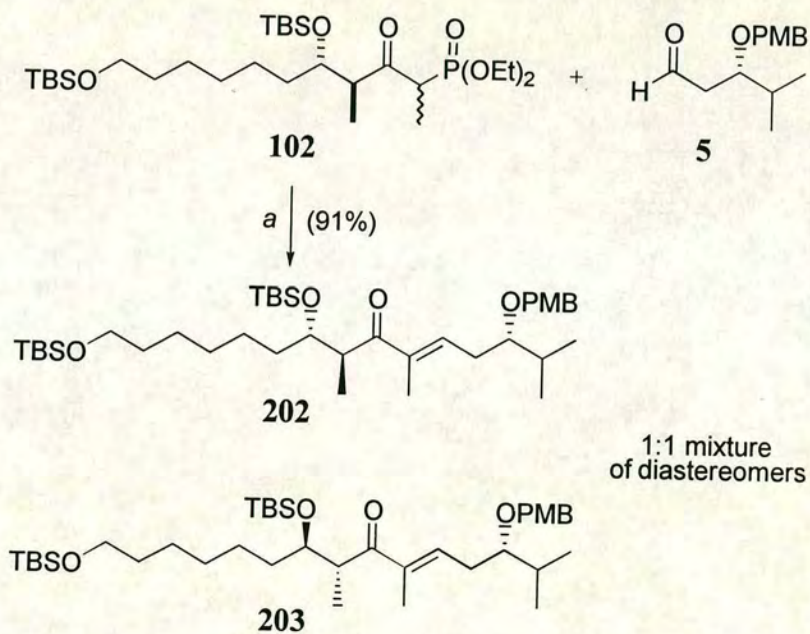
Scheme 94 Anionic displacement of ester **200**

As in **Section 2.4.1**, no attempt was made to separate the mixture of diastereomers (due to the epimeric centre at C(2)) as the mixture has been shown to give a single *E*-alkene product in the HWE reaction.

After careful chromatography a further amount of impure **201** (11%), was isolated, which was thought to contain the minor diastereomer from the aldol reaction (also an apparent *c.* 3:1 mixture at C(2)). This was confirmed after the HWE reaction of **201** with the aldehyde **5** gave a single diastereomer (see **Section 4.2.4**).

4.3.4 HWE Coupling: Construction of the C(10)-C(11) Bond

The barium hydroxide promoted HWE reaction had already been shown to be successful using isovaleraldehyde as a model for the aldehyde **5** in the studies discussed in **Chapter 2**, giving good yields of the *E*-trisubstituted enones.



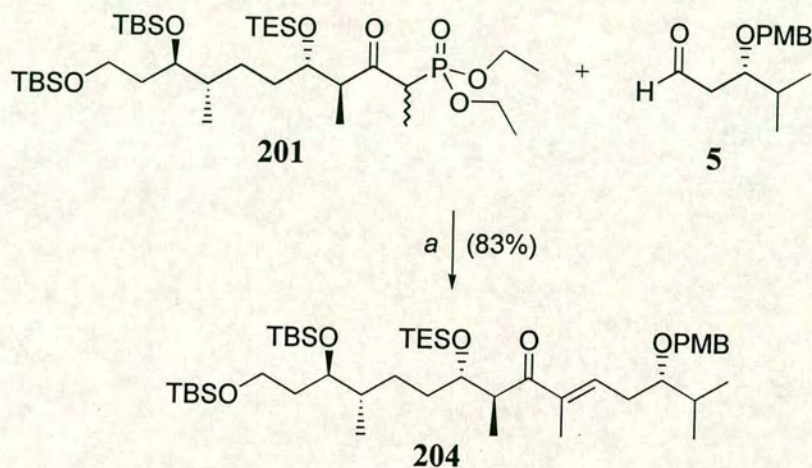
(a) i. Activated $\text{Ba}(\text{OH})_2 \cdot 8\text{H}_2\text{O}$, THF (aq.), rt, 30 min; ii. Aldehyde **5**, rt, 24 h.

Scheme 95 HWE reaction of aldehyde **5** and racemic phosphonate

In order to see if the previously optimised conditions could be used with the more complex β -substituted aldehyde **5**, its reaction with the racemic phosphonate

102 was attempted. The reaction proceeded smoothly to give 91% yield of a 1:1 diastereomeric mixture of the two compounds **202** and **203** (Scheme 95) with exclusive formation of the *E*-alkene.

In the case of the complex β -keto phosphonate **201**, required for the construction of the octalactin backbone; HWE coupling with aldehyde **5** gave the *E*-alkene **204** in 83% yield as a single diastereomer (Scheme 96).

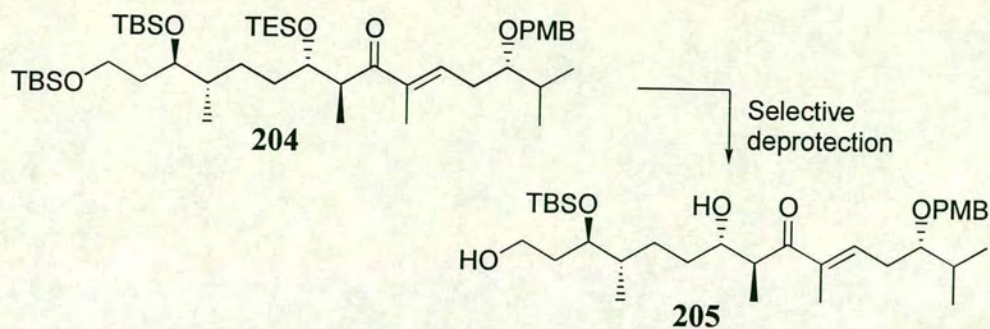


(a) i. Activated $\text{Ba}(\text{OH})_2 \cdot 8\text{H}_2\text{O}$, THF (aq.), rt, 40 min; ii. Aldehyde **5**, rt, 17 h.

Scheme 96 HWE of aldehyde **5** with phosphonate **201**

The formation of a single diastereomer indicated that removal of the diastereomeric impurity (from the aldol reaction) had successfully been achieved after the phosphonate displacement.

4.3.5 Deprotection of the HWE Adduct



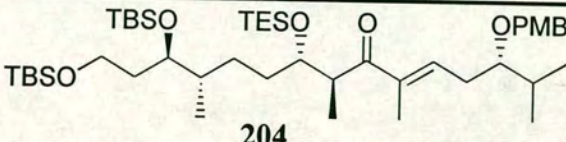
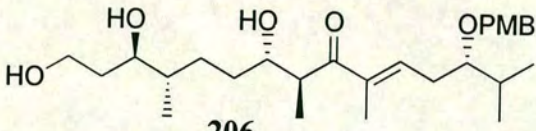
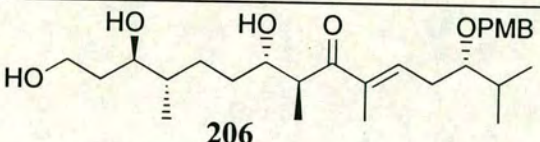
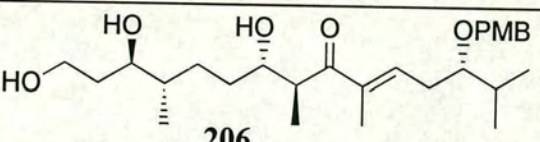
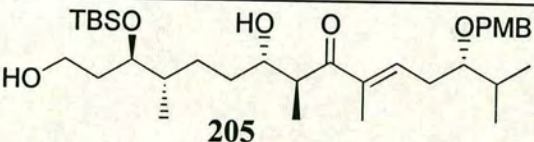
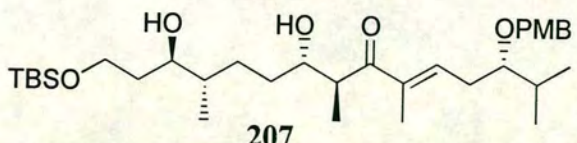
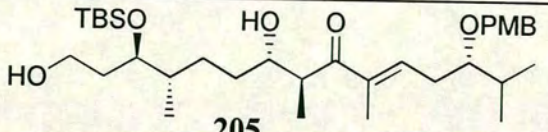
Entry	Conditions	Major product	Yield
1	AcOH/THF/H ₂ O (1:1:1)	 204	75%
		 206	19%
2	AcOH/THF/H ₂ O (3:1:1)	 206	90%
3	HF-Pyr, THF	 206	64%
4	TFA/THF/H ₂ O	 205	60%
		 207	11%
5	3HF.Et ₃ N, THF	 205	72%

Table 7 Selective desilylation of enone 204

Following the HWE reaction, the unmasking of the hydroxyls at the C(9) and C(15) centres in **204** was then necessary. Several methods were used in an attempt to selectively remove the primary TBS ether protecting group and the secondary TES ether whilst leaving intact the TBS ether on the secondary hydroxyl at C(13) and these results are summarised in **Table 7**.

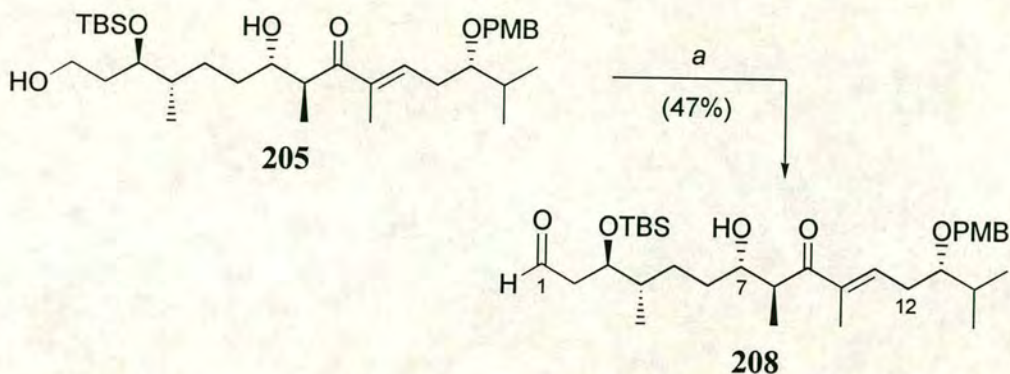
Precedent for the cleavage of a TES group in the presence of a TBS group using AcOH/H₂O/THF mixtures and HF-Pyr existed in the work of Seebach¹²⁷ and Masamune¹²⁸. Initial reactions using these reagents resulted in either no reaction or complete silyl deprotection to the triol **206** (**Table 7, entries 1-3**).

In the Merck synthesis of FK-506, the use of aqueous trifluoroacetic acid (TFA) resulted in the removal of a secondary TES group leaving a secondary TBS and other more acid stable silyl ethers intact.¹²⁹ Using three equivalents of TFA in THF/H₂O (6:1) resulted (after 6 h) in a 60% yield of the desired diol **205** plus 11% of a higher R_f spot which, after careful analysis of the 600 MHz ¹H NMR, was assigned as the TBS protected diol **207** (**entry 4**).

Using the conditions of Nicolaou¹³⁰ (3HF.Et₃N, THF, 0 °C to rt) resulted in a 72% yield of the desired diol **205** after 35 h at room temperature (**entry 5**). The absence of any silyl migration in this reaction is presumably due to the buffered nature of this desilylating reagent.

4.2.6 Selective Oxidation

Using the conditions optimised for the selective oxidation discussed in **Chapter 2** (TEMPO, NaOCl, NaBr, CH₂Cl₂, aq. NaHCO₃ (sat.), aq. NaCl (sat.), rt) oxidation of **205** resulted in a 47% yield of the desired aldehyde **208** (**Scheme 97**).



(a) TEMPO, NaOCl, NaBr, CH₂Cl₂, aq. NaHCO₃ (sat.), aq. NaCl (sat.), rt.

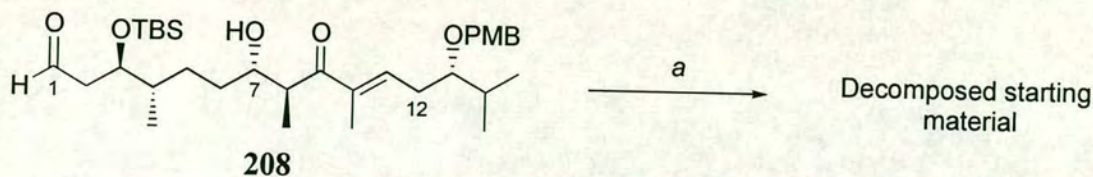
Scheme 97 Selective oxidation of diol **205**

Unfortunately, due to the instability of the aldehyde and the limited material available only IR and ¹H NMR evidence was available to confirm the production of the aldehyde **208**. However, the presence of OH, C=O (aldehyde) and C=O (α,β-unsaturated ketone) bands at 3444, 1721 and 1652 cm⁻¹ respectively in the IR indicate the formation of **208**. This, combined with the ¹H NMR data : C(1)H, (δ = 9.76, 1H, t); C(7)H (δ = 3.54, 1H, m); C(2)H₂ and C(12)H₂ (δ = 2.57-2.46, 4H, m) confirm no overoxidation to the diketone or the acid.

4.3.7 Evans-Tishchenko Cyclisation

It was envisaged that the reaction of aldehyde **208** with a Sm(II)/benzaldehyde pinacol adduct would result in an intramolecular Evans-Tishchenko reaction to give the lactone **209** (**Scheme 101**). It was also reasoned that the enhanced rate of reaction would limit the epimerisation of the centre α to the ketone at C(8) prior to cyclisation (this unwanted epimerisation was observed during the cyclisation of the simple aldehydes as discussed in **Chapter 2**).

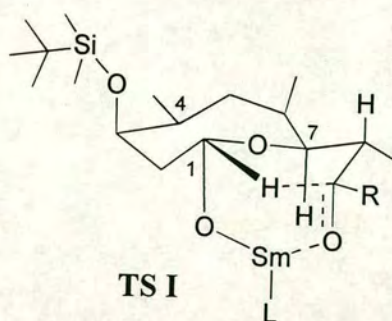
However, subjection of aldehyde **208** to the previously described conditions (30 mol% SmI_2 (0.1 M solution in THF)/benzaldehyde premixed in THF) resulted in no reaction. Addition of a further equivalent of the premixed samarium species gave no reaction by tlc and after 1 h decomposition of the starting aldehyde was observed (**Scheme 98**). Analysis of the crude ^1H NMR showed no evidence for the presence of a cyclised Evans-Tishchenko product.



(a) $\text{PhCHO}/\text{SmI}_2$ (premixed), THF, rt.

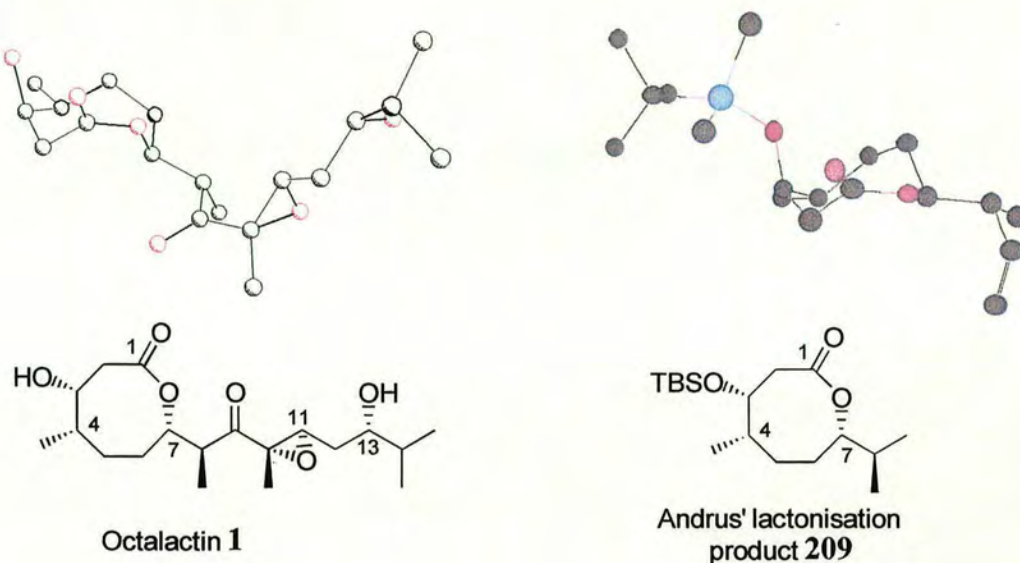
Scheme 98 Attempted intramolecular Evans-Tishchenko reaction

It is unclear why this reaction did not proceed to any extent as the presence of the bulky TBS group on the secondary hydroxyl β to the aldehyde and the methyl group should force the lactone into a favoured chair-boat conformation **TS I** (**Scheme 99**) as suggested by Andrus⁶⁶.



Scheme 99 Proposed transition state: chair-boat conformation

The chair-boat conformation has been shown to be the lowest energy conformation for many eight-membered ring compounds and is found in the crystal structure of octalactin A **1**.⁷



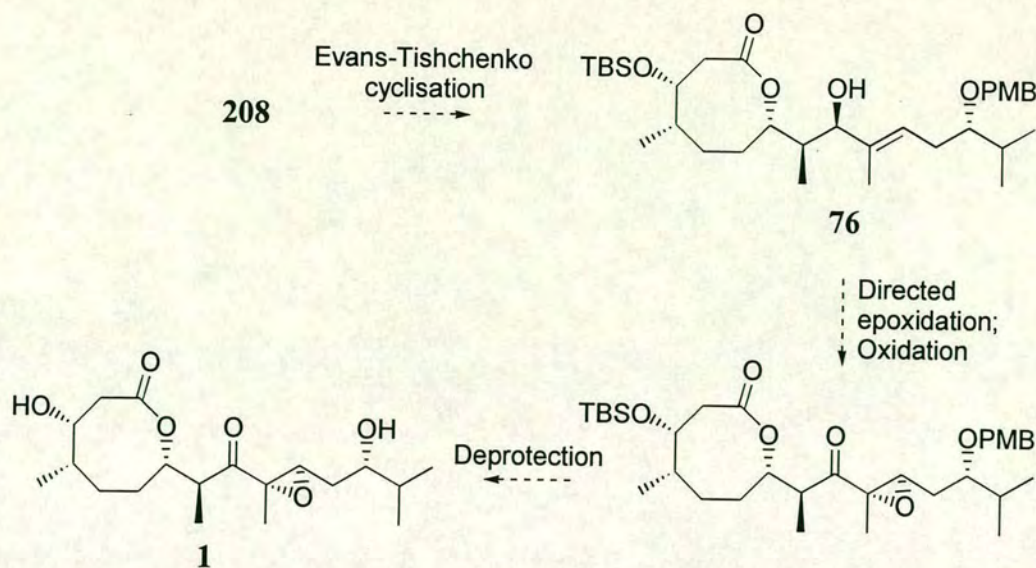
Scheme 100 X-ray crystal structure of octalactin A and MM2 calculated structure of Andrus' intermediate

The lactonisation product **209** of Andrus was subjected to MM2 calculations using ChemDraw 3D[®] and was shown to have the same chair-boat structure as that of octalactin A (crystal structure)[†] (**Scheme 100**).

Whether it is possible for the transition state of the samarium-catalysed Evans-Tishchenko to adopt this conformation would require more detailed modelling than was possible during the course of this thesis.

The failure of this reaction prohibited the final steps of the total synthesis which were to be pursued along the well precededented lines of Buszek⁶⁸ and Clardy⁷² (**Scheme 101**).

[†] Crystal structure obtained from the Cambridge Structural Database.



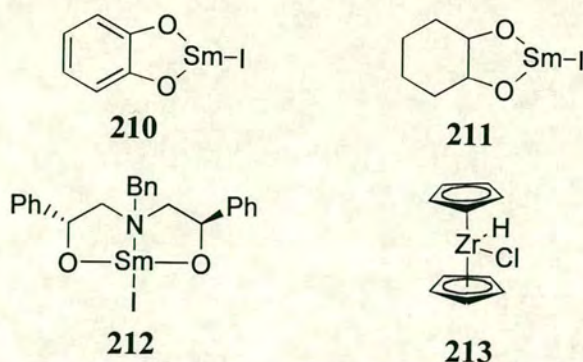
Scheme 101 Final steps of the total synthesis

4.3.8 Alternative Catalysts for the Evans-Tishchenko Reaction

Clearly, the need for a suitable Evans-Tishchenko catalyst for the intramolecular version of the reaction still exists, and remains of interest to the Hulme group.

Development of a samarium based catalyst should allow for the stereoselective formation of the lactone **76** and an improved understanding of the mechanism of the reaction.

Analysis of the species used successfully so far suggests the need for the presence of a bidentate dioxo ligand such as that formed by pinacolisation of the aldehyde (PhCHO). Therefore, catalysts such as **210**, resulting from catechol addition to a SmI₂ solution or **211** (*syn/anti* diastereomers) might lead to improved reactivity and/or higher turnover in the reaction. The Sm(III) catalyst **212** was used to catalyse the Meerwein-Pondorf-Verley reduction of aryl methylketones and may offer a further viable alternative (**Scheme 102**).¹³¹

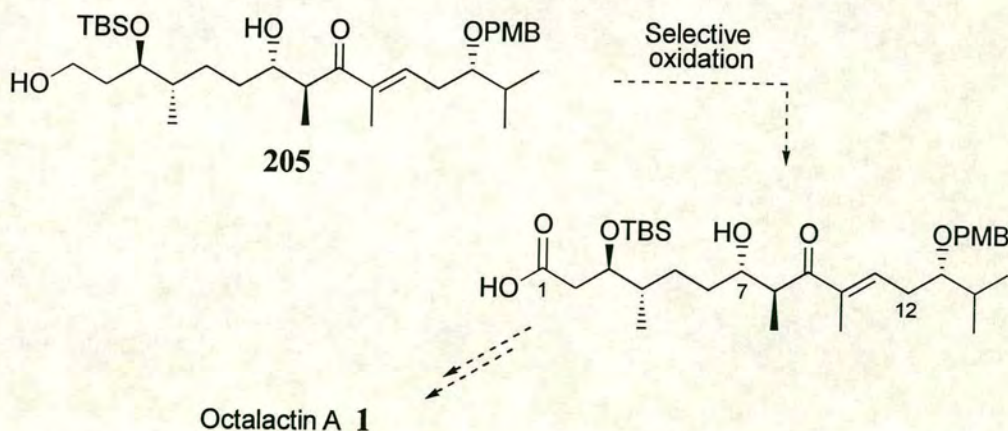


Scheme 102 Potential Evans-Tishchenko catalysts

Ishii⁶² has recently reported the use of a zirconocene based complex **213** as a catalyst in the Evans-Tishchenko reaction and this may provide another method for the reaction that could avoid any unwanted side-reactions caused by the presence of Sm(II) species. Despite this, the zirconocene based catalyst **213** remains unexploited in complex natural product synthesis.

4.2.9 Conclusions

A successful synthesis of the C(1)-C(15) carbon backbone of octalactin A has been demonstrated with the synthesis of **205** and the required stereocentres at C(3), C(4), C(7), C(8) and C(13) in place.



Scheme 103 Proposed alternative route to octalactin A

The diol **205** could be used in the synthesis of octalactin A, either through a successful Evans-Tishchenko type coupling as discussed in **Section 4.2.7** or by elaboration of the backbone to the acid, lactonisation and appropriate functionalisation (**Scheme 103**).

CHAPTER 5**EXPERIMENTAL PROCEDURES****5.1 GENERAL EXPERIMENTAL**

¹H nuclear magnetic resonance (NMR) spectra were recorded using an internal deuterium lock for the indicated reference at ambient probe temperatures on Bruker AC200 (200 MHz), Varian Gemini 200 (200 MHz), Bruker AC250 (250 MHz), Bruker AM360 (360 MHz) or Varian Inova 600 (600 MHz) Fourier transforms instruments. The data is presented as follows: chemical shift (in ppm on the δ scale relative to $\delta_{\text{TMS}} = 0$), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet, br = broad), coupling constant and the interpretation. ¹³C NMR spectra were recorded using an internal deuterium lock for the indicated reference at ambient probe temperatures on Varian Gemini 200 (50.3 MHz), Bruker AC250 (62.9 MHz) or Varian Inova 600 (150 MHz) instruments and are reported in ppm on the δ scale. Where Distortionless Enhancement Polarisation Transfer (DEPT) spectra have been recorded, the carbon signals due to methyl (CH₃), methylene (CH₂), methine (CH) and quaternary carbon (C) are assigned.

Infra-red spectra were recorded on a Biorad FTS-7 or a Perkin Elmer Paragon 1000 FT-IR instrument using 5mm sodium chloride plates, or 0.1 mm sodium chloride solution cells. The wavelengths of maximum absorbance (ν_{max}) are quoted in cm⁻¹. Electron impact (EI) mass spectra were obtained using a Finnigan 4500 mass spectrometer and fast atom bombardment performed on a Kratos MS50TC by the service at the University of Edinburgh Chemistry department. All other mass spectra were run by the EPSRC service at Swansea. The parent ion or fragment of highest mass is quoted, followed by significant fragments with relative intensities. Optical rotations were measured on a on an AA-1000 polarimeter with a path length of 0.5 dm at the sodium D line (589 nm) and are reported as follows:

$[\alpha]_D^{23}$ concentration (c in g/100 ml) and solvent (all optical rotations were measured at a temperature of 23 °C). Melting points were determined on a Gallenkamp Electrothermal Melting Point apparatus and are uncorrected. Elemental analysis was carried out by the service at the University of Edinburgh Chemistry department on a Perkin Elmer 2400 CHN Elemental Analyser. Tlc was performed on Merck 60F₂₅₄ (0.25 mm) glass backed silica plates and visualised by ultraviolet light and/or anisaldehyde* or molybdate[†] stain. Flash chromatography was carried out on Merck Kieselgel 60 (Merck 9385) under positive pressure by means of an air line or a hand pump (the use of this term also implies the removal of the solvent afterwards under reduced pressure). Eluent compositions are quoted as v/v ratios. High performance liquid chromatography (HPLC) was carried out on a Gilson instrument using a Spherisorb column (internal diameter: 20 mm) and equipped with a Gilson refractive index detector. A standard flow rate of 10 ml/min was used. Chiral HPLC was performed using a Waters instrument with a Chiracel OD column (internal diameter: 4.6 mm) equipped with a UV detector. A standard flow rate of 0.5 ml/min was used. All solvents to be used for HPLC analysis were vacuum filtered and degassed prior to use. All HPLC samples were filtered through 0.45 µm nylon syringe filters prior to analysis.

Reagents were purified by standard means.¹³² Dichloromethane (CH₂Cl₂), hexane, and cyclohexene were distilled from calcium hydride prior to use under an argon atmosphere. Tetrahydrofuran (THF) and diethyl ether were distilled from sodium metal/benzophenone ketyl and stored under an argon atmosphere. The amine bases: triethylamine, diisopropylamine, diisopropylethylamine, pyridine and 2,6-lutidine were distilled from calcium hydride and stored over calcium hydride. The achiral aldehydes: isovaleraldehyde and isobutyraldehyde were freshly distilled from calcium chloride immediately prior to use; acetyl and propionyl chloride were distilled immediately prior to use. Methyl iodide was passed through a short column of alumina prior to use. Geraniol (dissolved in a small amount of CH₂Cl₂) and ^tbutyl

* Anisaldehyde dip prepared as follows: to EtOH (930 ml) was added slowly sulphuric acid (35 ml, 98%) followed by AcOH (10 ml) and finally *p*-anisaldehyde (2.5 ml).

[†] Molybdate dip prepared as follows: to H₂O (950 ml) was added slowly sulphuric acid (50 ml, 98%) followed by ammonium molybdate (50 g) and finally ceric sulfate (3 g).

hydroperoxide were dried over 4Å molecular sieves for at least two hours before use. ⁿButyl lithium (ⁿBuLi) and ^tButyl lithium (^tBuLi) solutions were titrated against *N*-pivaloyl-*o*-toluidine in solution in THF at ambient temperature immediately prior to use. All other reagents were used as supplied except where otherwise stated in the experimental text. Saturated aqueous solutions of inorganic salts are represented as: salt (volume; sat.).

All experiments were performed in an inert atmosphere of argon under anhydrous conditions using oven dried apparatus cooled in a desiccator or flame dried under argon prior to use, and employing standard techniques for the handling of air-sensitive materials.¹³³

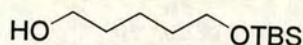
Index of General Procedures

General Procedure A:	Monoprotection of 1,n-diols	110
General Procedure B:	Oxidation of monoprotected 1,n-diols	112
General Procedure C:	<i>Anti</i> aldol; dicyclohexylbromoborane	116
General Procedure D:	Silyl protection of aldol adducts	121
General Procedure E:	Phosphonate displacement	126
General Procedure F:	Horner Wadsworth Emmons (HWE)	131
General Procedure G:	Desilylation of HWE adducts	136
General Procedure H:	Selective oxidation	139

5.2 EXPERIMENTAL FOR CHAPTER 2

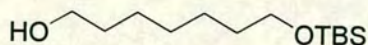
General procedure A: Monoprotection of 1,n-diols

The 1,n-diol (7.00 mmol) was added to a suspension of sodium hydride (7.00 mmol, 60% dispersion in mineral oil prewashed with dry hexane) in THF (10 ml) and stirred for 50 min at room temperature. TBSCl (7.00 mmol) was added in one portion and the reaction stirred for a further 45 min. The solution was poured into diethyl ether (90 ml), washed with K_2CO_3 (50 ml; 10% aqueous), NaCl (50 ml; sat.), dried ($MgSO_4$), and the solvent removed under reduced pressure. The resulting oil could then be purified by flash chromatography (30% EtOAc in hexane) to afford the monoprotected diol.

5-*t*-Butyldimethylsilyloxypentan-1-ol 80

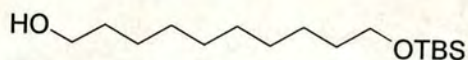
General procedure A was used with pentane-1,5-diol (1.71 ml, 16.33 mmol), sodium hydride (653 mg, 16.33 mmol) and TBSCl (2.46 g, 16.33 mmol) in THF (30 ml). Flash chromatography (30% EtOAc in hexane) afforded the monosilylated diol **80** as a clear, colourless oil (2.50 g, 72%). R_f (20% EtOAc in hexane) 0.33; ν_{max} (neat)/ cm^{-1} 3357 (OH); 1H NMR δ (200 MHz, $CDCl_3$) 3.64-3.53 (4H, m, CH_2OH and CH_2OTBS), 1.70-1.39 (6H, m, 3 x CH_2), 0.84 (9H, s, *t*-BuSi), 0.00 (6H, s, $SiMe_2$); ^{13}C NMR δ (62.9 MHz, $CDCl_3$) 63.0, 62.5, 32.3 (2C), 25.8 (3C), 21.8, 18.2, -5.5 (2C); m/z (EI) M^+ not found, 115 ($[t-BuMe_2Si]^+$ 40), 75 (100%).

1H NMR and ^{13}C NMR spectroscopic data in agreement with the literature.⁷⁴

7-*t*-Butyldimethylsilyloxyheptan-1-ol **81**

General procedure A was followed with heptane-1,7-diol (7.00 g, 52.9 mmol), sodium hydride (2.12 g, 52.9 mmol) and TBSCl (7.98 g, 52.9 mmol) in THF (150 ml). Flash chromatography (30% EtOAc in hexane) afforded the monosilylated diol **81** as a clear, colourless oil (7.66 g, 57%). R_f (20% EtOAc in hexane) 0.29; ν_{\max} (neat)/ cm^{-1} 3371 (OH); $^1\text{H NMR}$ δ (200 MHz, CDCl_3) 3.66-3.51 (4H, m, CH_2OH and CH_2OTBS), 1.72-1.35 (10H, m, 5 x CH_2), 0.85 (9H, s, *t*-BuSi), 0.00 (6H, s, SiMe_2); $^{13}\text{C NMR}$ δ (50.3 MHz, CDCl_3) 63.1, 62.6, 32.6, 32.5, 29.1, 25.8 (3C), 25.6 (2C), 18.2, -5.5 (2C).

$^1\text{H NMR}$ and $^{13}\text{C NMR}$ spectroscopic data in agreement with the literature.⁷⁴

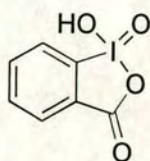
10-*t*-Butyldimethylsilyloxydecan-1-ol **82**

General procedure A was used with decane-1,10-diol (1.99 g, 11.75 mmol), sodium hydride (0.47 g, 11.75 mmol) and TBSCl (1.77 g, 11.75 mmol) in THF (25 ml). Flash chromatography (30% EtOAc in hexane) afforded the monosilylated diol **82** as a clear, colourless oil (1.68 g, 49%). R_f (20% EtOAc in hexane) 0.33; ν_{\max} (neat)/ cm^{-1} 3341 (OH); $^1\text{H NMR}$ δ (200 MHz, CDCl_3) 3.65-3.48 (4H, m, CH_2OH and CH_2OTBS), 1.61-1.18 (16H, m, 8 x CH_2), 0.85 (9H, s, *t*-BuSi), 0.00 (6H, s, SiMe_2).

$^1\text{H NMR}$ spectroscopic data in agreement with the literature.⁷⁴

General procedure B: Oxidation of monoprotected 1,n-diols

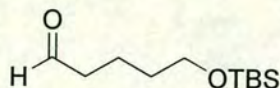
The alcohol (0.89 mmol) was dissolved in THF (2 ml) and added to a clear solution of IBX (495 mg, 1.77 mmol) in DMSO (2 ml) and the solution stirred at room temperature in a stoppered flask for 1.5h. H₂O (30 ml) was added and the white precipitate removed by filtration. The solution was extracted with EtOAc (3 x 20 ml), dried (MgSO₄), the solvent removed under reduced pressure and the residue purified by flash chromatography (30% EtOAc in hexane).

Synthesis of Iodoxybenzoic acid (IBX) **83**

*The synthesis of **83** should be handled with care.*^δ

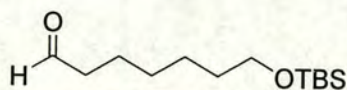
To a vigorously stirred (large stirrer bar or mechanical stirrer is preferred) mixture of 2-iodobenzoic acid (51.4 g, 206 mmol) and H₂SO₄ (1000 ml of a 0.72 M aqueous solution) at 55 °C was added potassium bromate (45.0 g, 269 mmol) portion-wise over 0.5 h. The mixture was stirred for 3.5 h at 70 °C and then cooled in an ice bath. The solid precipitate was then filtered and washed sequentially with H₂O, acetone and Et₂O (all 1000 ml) and dried to give an off-white solid **83** (49.6 g, 88%). MP 231-233 °C, lit.⁷⁷ 233 °C.

^δ Whilst IBX has been reported to be explosive similar to trinitrotoluene, the procedure given here removes any residual traces of bromine thought to be the cause of the explosive samples prepared by ICI.⁷⁷

5-*t*-Butyldimethylsilyloxypentanal 84

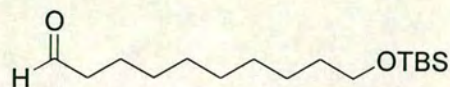
General procedure B was used for monoprotected alcohol **80** (1.07 g, 4.92 mmol) and IBX (2.48 g, 8.86 mmol) in DMSO (15 ml) and THF (5 ml) and stirred for 1 h. Flash chromatography (20% EtOAc in hexane) gave the aldehyde as a clear, colourless oil (846 mg, 80 %) which was characterised by ^1H NMR and used immediately due its inherent instability. R_f (20% EtOAc in hexane) = 0.56; ν_{max} (neat)/ cm^{-1} 2720 (C-H, aldehyde) 1727 (C=O); ^1H NMR δ (200 MHz, CDCl_3) 9.73 (1H, t, J = 1.8 Hz, $\text{HC}(\text{O})$), 3.69 (2H, t, J = 6.4 Hz, CH_2OTBS), 2.43 (2H, td, J = 6.6 Hz and 1.8 Hz, $\text{CH}_2\text{C}(\text{O})$), 1.70-1.43 (4H, m, 2 x CH_2), 0.86 (9H, s, *t*-BuSi), 0.02 (6H, s, SiMe_2).

^1H NMR spectroscopic data in agreement with the literature.¹³⁴

7-*t*-Butyldimethylsilyloxyheptanal 85

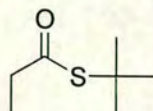
General procedure E was used for monoprotected alcohol **81** (697 mg, 2.83 mmol) and IBX (1.32 g, 4.72 mmol) in DMSO (10 ml) and THF (3 ml) and stirred for 1.5 h. Flash chromatography (10% EtOAc in hexane) gave aldehyde **85** as a clear, colourless oil (846 mg, 90 %) which was characterised by ^1H NMR and used immediately due its instability. R_f (20% EtOAc in hexane) = 0.65; ν_{max} (neat)/ cm^{-1} 2714 (C-H, aldehyde) 1727 (C=O); ^1H NMR δ (200 MHz, CDCl_3) 9.75 (1H, t, J = 1.8 Hz, $\text{HC}(\text{O})$), 3.58 (2H, t, J = 6.4 Hz, CH_2OTBS), 2.41 (2H, td, J = 6.3 Hz and 1.8 Hz, $\text{CH}_2\text{C}(\text{O})$), 1.62-1.18 (8H, m, 4 x CH_2), 0.87 (9H, s, *t*-BuSi), 0.02 (6H, s, SiMe_2).

^1H NMR spectroscopic data in agreement with the literature.¹³⁵

10-*t*-Butyldimethylsilyloxydecanal **86**

General procedure B was used for monoprotected alcohol **82** (2.29 g, 7.92 mmol) with IBX (3.99 g, 14.3 mmol) in DMSO (25 ml) and THF (25 ml) and stirred for 1.5 h. Flash chromatography (20% EtOAc in hexane) gave the aldehyde **86** as a clear, colourless oil (1.92 g, 85 %) which was characterised by ^1H NMR and used immediately due its instability. R_f (20% EtOAc in hexane) = 0.68; ν_{max} (neat)/ cm^{-1} 2718 (C-H, aldehyde) 1729 (C=O); ^1H NMR δ (200 MHz, CDCl_3) 9.72 (1H, t, J = 1.8 Hz, HC(O)), 3.56 (2H, t, J = 6.2 Hz, CH_2OTBS), 2.43 (2H, td, J = 7.3 Hz and 1.8 Hz, $\text{CH}_2\text{C(O)}$), 1.72-1.20 (14H, m, 7 \times CH_2), 0.86 (9H, s, *t*-BuSi), 0.00 (6H, s, SiMe_2).

^1H NMR spectroscopic data in agreement with the literature.¹³⁶

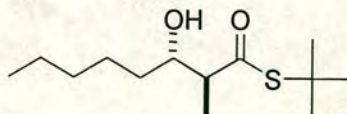
***t*-Butylpropanthioate 88**

Triethylamine (11.2 ml, 80 mmol) was added slowly to a solution of *t*-butylthiol (STENCH) (9.0 ml, 80 mmol) in ether (100 ml) at 0 °C. Propionyl chloride (7.0 ml, 80 mmol) was then added slowly over 15-20 min and the milky white ether solution stirred at room temperature for 51 h. The solution was washed with H₂O (100 ml), 0.1 N NaOH (100 ml), H₂O (100 ml) and NaCl (100 ml; sat.). The organics were dried (MgSO₄) and the volatiles removed under reduced pressure. The product was purified by vacuum distillation, affording thioester **88** as a clear, pungent oil. (7.49 g, 64%), BP 52 °C (12 mm Hg), lit.¹³⁷ 96-97 °C (100 mmHg), *R_f* (20% EtOAc in hexane) = 0.61; ¹H NMR δ (250 MHz, CDCl₃) 2.45 (2H, q, *J* = 7.4 Hz, CH₂), 1.45 (9H, s, *t*-Bu), 1.12 (3H, t, *J* = 7.4 Hz, CH₃).

¹H NMR spectroscopic data in agreement with the literature.¹³⁸

Preparation of lithiumdiisopropylamide (LDA) solution

To a solution of diisopropylamine (424 mg, 4.19 mmol) in THF (4 ml) was added ⁿBuLi (2.54 ml, 3.94 mmol, 1.55 M solution in hexanes) dropwise at -78 °C and the reaction warmed to 0°C for 15 minutes with stirring. The reaction mixture was recooled to -78 °C and used immediately.

***t*-Butyl (2*SR*,3*SR*)-3-hydroxy-2-methyloctanthioate 92****METHOD A:**

To a freshly prepared solution of LDA (3.94 mmol) in THF (4 ml) at -78 °C, thioester **88** (359 mg, 2.46 mmol) was added and the reaction stirred for 40 min

before adding TMSCl^\dagger (1.5 ml, 11.8 mmol) and stirred for a further 20 min. The reaction mixture was quenched with pH 7 phosphate buffer (5 ml), extracted with pentane (30 ml) added and the organics were washed with pH 7 buffer (2 x 25 ml). The aqueous washings were re-extracted with pentane (30 ml), the organics combined, dried (MgSO_4) and the volatiles removed under reduced pressure. The silyl ketene acetal (536 mg, 2.46 mmol) was dissolved in CH_2Cl_2 (20 ml) with hexanal (62 mg, 0.62 mmol) and cooled to -78°C before adding $\text{BF}_3\cdot\text{OEt}_2$ (303 ml, 2.46 mmol) dropwise and stirred for 2 h at that temperature. The reaction was quenched by addition of pH 7 phosphate buffer (5 ml), the organics washed with buffer (2 x 25 ml) and the aqueous washings re-extracted with CH_2Cl_2 (2 x 15 ml). The organic extracts were combined, dried (MgSO_4) and the volatiles removed under reduced pressure to give a yellow oil which was purified by flash chromatography (5-25% EtOAc/hexane) to give **92** as a clear, colourless oil (145mg, 97%).

Preparation of dicyclohexylbromoborane $(\text{Chx})_2\text{BBr}$

Monobromoborane.methyl sulfide complex (3.61 ml, 33.8 mmol) was added dropwise to a solution of cyclohexene (7.2 ml, 71 mmol) in CH_2Cl_2 (50 ml) at 0°C , and the reaction stirred for 2.5 h at 0°C followed by 13 h at room temperature without stirring. The solvent was removed under reduced pressure (water pump pressure) to give a colourless solid which was purified by distillation to give a clear oil $^\phi$ (4.82 g, 55%). BP 122°C (2mm Hg), lit.¹⁶ 120°C (1.5 mmHg)

General procedure C: *Anti* aldol; dicyclohexylbromoborane

To a solution of thioester **88** (219 mg, 1.50 mmol) and dicyclohexylbromoborane (416 mg, 1.70 mmol) in ether (5 ml) at 0°C was added followed triethylamine (218 mg, 1.80 mmol). The reaction mixture was stirred for 2.5 h at that temperature before

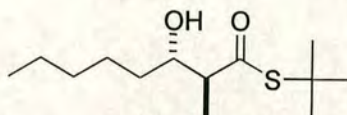
† The TMSCl was distilled from K_2CO_3 and mixed with an equal volume of Et_3N prior to use (this was found to remove any residual HCl). The precipitate of $\text{Et}_3\text{N}\cdot\text{HCl}$ was removed by centrifugation and the solution taken as being an equimolar mixture of Et_3N and TMSCl .

$^\phi$ The air and moisture sensitive bromoborane could be stored for several months under argon in the fridge without substantial loss of activity and was redistilled when it became yellow in colour.

cooling to $-78\text{ }^{\circ}\text{C}$. The aldehyde (1.00 mmol) was added dropwise, and the reaction stirred for a further 3 h when deemed complete by tlc.

OXIDATIVE WORK UP: Phosphate buffer (pH 7; 8 ml) was added, the mixture was extracted with CH_2Cl_2 (2 x 20 ml) and the organics cooled to $0\text{ }^{\circ}\text{C}$. MeOH (30 ml) and H_2O_2 (10 ml; 30% aqueous) were added and the solution stirred for 1 h. H_2O (20 ml) was added and the reaction mixture extracted with CH_2Cl_2 (2 x 30 ml). The organics were washed with saturated NaHCO_3 (50 ml; sat.), NaCl (50 ml; sat.), dried (MgSO_4), the volatiles removed under reduced pressure and the residue purified by flash chromatography (5-20% EtOAc in hexane).

***t*-Butyl (2*SR*,3*SR*)-3-hydroxy-2-methyloctanthioate 92**



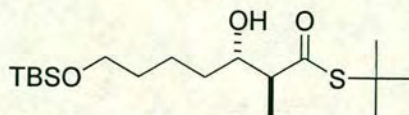
METHOD B: (Boron enolate)

General procedure C was followed with thioester **88** (239 mg, 1.64 mmol), dicyclohexylbromoborane (498 mg, 2.04 mmol) and triethylamine (218 mg, 2.16 mmol). After cooling to $-78\text{ }^{\circ}\text{C}$, hexanal (120 mg, 1.2 mmol) was added dropwise, and the reaction stirred for a further 3 h. Oxidative work up gave the crude aldol product which was purified by flash chromatography (5% EtOAc in hexane) to give the aldol adduct (188 mg, 64%) as a clear oil. Analysis of the 250 MHz ^1H NMR spectra showed the presence of a single diastereomer, the *anti* aldol adduct. R_f (20% EtOAc in hexane) = 0.64; ν_{max} (neat)/ cm^{-1} 3454 (OH) and 1674 (C=O); ^1H NMR δ (250 MHz, CDCl_3) 3.63-3.48 (1H, m, C(3)H), 2.62 (1H, qd, $J = 7.0$ & 5.6 Hz, C(2)H), 2.46 (1H, d, $J = 7.5$ OH), 1.45 (9H, s, *t*-BuS), 1.42-1.22 (8H, m, 4 x CH_2), 1.21 (3H, d, $J = 7.0$ Hz, C(2) CH_3), 0.87 (3H, t, $J = 6.3$ Hz, C(8) H_3); ^{13}C NMR δ (62.9 MHz, CDCl_3) 204.0, 72.7, 52.1, 46.9, 33.6, 30.3, 28.3 (3C), 23.9, 21.1, 13.9 and 12.6.

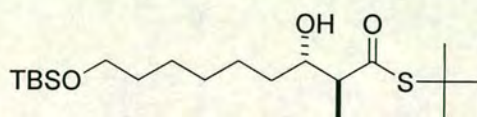
^1H NMR spectroscopic data in agreement with the literature.⁸¹

t-Butyl (2*SR*,3*SR*)-7-*t*-butyldimethylsilyloxy-3-hydroxy-2-methylheptanthioate

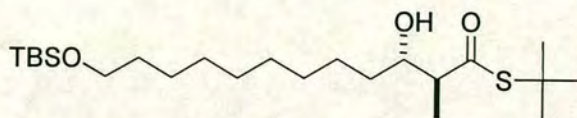
89



General procedure C was used with thioester **88** (861 mg, 5.90 mmol), dicyclohexylbromoborane (1.64 g, 6.69 mmol) and triethylamine (984 ml, 7.08 mmol) added. After cooling to -78 °C aldehyde **84** (846 mg, 3.92 mmol) was added dropwise, and the reaction stirred for a further 3 h. Oxidative work up gave the crude aldol product which was purified by flash chromatography (gradient elution, 1-20% EtOAc in hexane) to give the aldol adduct **89** as a clear, colourless oil (1.17 g, 83%). Analysis of the 250 MHz ^1H NMR showed the presence of a single diastereomer, the *anti* aldol product **89**. R_f (20% EtOAc in hexane) = 0.61 ; ν_{max} (neat)/ cm^{-1} 3459 (OH), 1675 (C=O); ^1H NMR δ (250 MHz, CDCl_3) 3.60-3.54 (3H, m, CHOH and CH_2OTBS), 2.58 (1H, qd, $J = 7.0$ & 5.7 Hz, C(2) H), 2.34 (1H, brs, OH), 1.56-1.34 (6H, m, 3 x CH_2), 1.42 (9H, s, *t*-BuS), 1.17 (3H, d, $J = 7.0$ Hz, C(2) CH_3), 0.85 (9H, s, *t*-BuSi), 0.00 (6H, s, SiMe_2); ^{13}C NMR δ (62.9 MHz, CDCl_3) 205.0 (C), 73.9 (CH), 62.9 (CH_2), 53.4 (CH), 48.1 (C), 34.7 (CH_2), 32.5 (CH_2), 29.6 (3 CH_3), 25.8 (3 CH_3), 21.9 (CH_2), 18.2 (C), 15.1 (CH_3), -5.2 (CH_3), -5.8 (CH_3); HRMS (FAB, MeCN/thioglycerol) $[\text{M}+\text{H}]^+$ found 363.2389, $\text{C}_{18}\text{H}_{39}\text{O}_3\text{SSi}$ requires 363.2389; m/z 363 ($[\text{M}+\text{H}]^+$ 52), 273 (100%).

***t*-Butyl (2*SR*,3*SR*)-9-*t*-butyldimethylsilyloxy-3-hydroxy-2-methylnonanthioate 90**

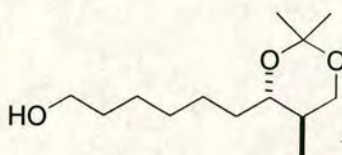
General procedure C was used with thioester **88** (887 mg, 6.08 mmol), dicyclohexylbromoborane (1.78 g, 7.29 mmol) and triethylamine (1.07 ml, 7.72 mmol). After cooling to -78 °C aldehyde **85** (619 mg, 2.54 mmol) was added and the reaction mixture stirred for a further 2.5 h. Flash chromatography (gradient elution, 5-10% EtOAc in hexane) gave the aldol adduct **90** as a clear, colourless oil (655 mg, 71%). Analysis of the 200 MHz ^1H NMR showed the presence of a single diastereomer, the *anti* aldol product. R_f (20% EtOAc in hexane) = 0.53; ν_{max} (neat)/ cm^{-1} 3470 (OH), 1670 (C=O); ^1H NMR δ (200 MHz, CDCl_3) 3.58-3.52 (3H, m, CHOH and CH_2OTBS), 2.58 (1H, qd, $J = 7.0$ & 5.5 Hz, C(2)*H*), 2.20 (1H, br s, OH), 1.46-1.21 (10H, m, 5 x CH_2), 1.43 (9H, s, *t*-BuS), 1.17 (3H, d, $J = 7.0$ Hz, C(2) CH_3), 0.85 (9H, s, *t*-BuSi), 0.00 (6H, s, SiMe_2); ^{13}C NMR δ (50.3 MHz, CDCl_3) 205.2, 73.8, 62.9, 53.5, 48.0, 34.8, 32.5, 29.6 (3C), 29.1, 25.8 (3C), 25.6, 23.9, 18.2, 15.2, -5.3 (2C); HRMS (FAB, MeCN/thioglycerol) $[\text{M}+\text{H}]^+$ found 391.2701, $\text{C}_{20}\text{H}_{43}\text{O}_3\text{SSi}$ requires 391.2702; m/z 391 ($[\text{M}+\text{H}]^+$ 22), 301 (37%).

***t*-Butyl(2*SR*,3*SR*)-12-*t*-butyldimethylsilyloxy-3-hydroxy-2-methyldodecanthioate 91**

General procedure C was used with thioester **88** (1.47 g, 10.05 mmol), dicyclohexylbromoborane (2.79 g, 11.40 mmol) and triethylamine (1.72 ml, 12.06 mmol). After cooling to -78 °C aldehyde **86** (1.92 g, 2.54 mmol) in ether (5 ml + 5 ml washings) was added and the reaction mixture stirred for a further 1.5 h.

Oxidative work up gave the crude aldol product which was purified by flash chromatography (5% EtOAc in hexane) to give the crude aldol adduct **91** as a clear, colourless oil (1.92 g, 66%) which was used without further purification. Analysis of the 200 MHz ^1H NMR showed the presence of a single diastereomer, the *anti* aldol product. R_f (20% EtOAc in hexane) = 0.53; ν_{max} (neat)/ cm^{-1} 3462 (OH), 1673 (C=O); ^1H NMR δ (200 MHz, CDCl_3) 3.63-3.51 (3H, m, CHOH and CH_2OTBS), 2.58 (1H, qd, $J = 7.0$ & 5.5 Hz, C(2)*H*), 1.96 (1H, br s, OH), 1.49-1.21 (16H, m, 8 x CH_2), 1.43 (9H, s, *t*-BuS), 1.17 (3H, d, $J = 7.0$ Hz, C(2) CH_3), 0.85 (9H, s, *t*-BuSi), 0.00 (6H, s, SiMe_2); m/z 432 ($[\text{M}+\text{H}]^+$ 18), 342 (42%).

(5*SR*,6*SR*)-6-(6'-Hydroxyhexanyl)-2,2,5-trimethyl-1,3-dioxane **93**



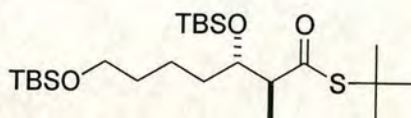
To a solution of aldol adduct **90** (90 mg, 0.231 mmol) in THF (2 ml) was added LiBH_4 (15 mg, 0.692 mmol) portionwise at 0 °C and the reaction allowed to warm to room temperature before being stirred for a further 1.5 h. To the reaction mixture was added carefully NH_4Cl (5ml; sat.) and the mixture extracted with CH_2Cl_2 (2 x 6 ml), the organics combined, washed with NaCl (10 ml; sat.), dried (MgSO_4) and the volatiles removed under reduced pressure to give the corresponding 1,3-diol as a clear oil (69 mg, 98%). To a solution of the crude diol (69 mg, 0.227 mmol) in DMF (1 ml) was added $\text{TsOH}\cdot\text{H}_2\text{O}$ (4 mg, 2.1 μmol) and 2,2-dimethoxypropane (126 μl , 1.02 mmol) and the reaction stirred for 72 h at room temperature. The reaction was quenched by the addition of NaCl (3ml; sat.) and the mixture extracted with CH_2Cl_2 (2 x 5 ml). The organics were combined, dried (MgSO_4) and the volatiles removed under reduced pressure. Flash chromatography (10%-50% EtOAc in hexane) gave the acetonide **93** as a clear oil (36 mg, 68%). R_f (20% EtOAc in hexane) = 0.23; ^1H NMR δ (600 MHz, CDCl_3) 3.66 (1H, dd, $J = 11.5$ & 5.2 Hz, C(4) H_AH_B), 3.47 (1H, app t, $J = 11.5$ Hz, C(4) H_AH_B), 3.41 (1H, ddd, $J = 12.4$, 8.3 & 2.5 Hz, C(6)*H*), 3.36

(2H, t, $J = 6.8$ Hz, C(6')H₂), 1.66-1.24 (11H, C(5)H and 5 x CH₂), 1.40 (3H, s, C(2)CH₃), 1.36 (3H, s, C(2)CH₃), 0.72 (3H, d, $J = 6.6$ Hz, C(5)HCH₃); ¹H NMR decoupling experiments δ (600 MHz, CDCl₃) Irradiation at 3.66 led to simplification at 3.47 and 1.66-1.24, irradiation at 3.47 led to simplification at 3.66 and 1.62, irradiation at 3.41 led to simplification at 1.62-1.24 and irradiation at 0.72 caused simplification at 1.66-1.24; ¹³C NMR δ (62.9 MHz, CDCl₃) 98.0 (C), 74.8 (CH), 66.1 (CH₂), 60.1 (CH₂), 33.9 (CH), 32.8 (CH₂), 29.9 (CH₂), 29.7 (CH₃), 29.4 (CH₂), 26.3 (CH₂), 24.8 (CH₂), 19.0 (CH₃), 12.7 (CH₃).

General Procedure D: TBS protection of aldol adducts

To a solution of the the aldol adduct (9.00 mmol) in DMF (10 ml) was added imidazole (2.49 g, 6.00 mmol) and TBSCl (2.71 g, 18.00 mmol) and the reaction mixture stirred for 24 h at room temperature when deemed complete by tlc. NaCl (30 ml; sat.) was added and the mixture extracted with EtOAc (3 x 50 ml). The organics were dried (MgSO₄), the volatiles removed under reduced pressure and the residue purified by flash chromatography (2% EtOAc in hexane).

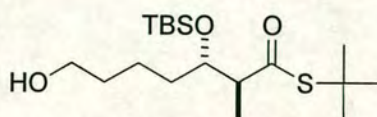
t-Butyl (2*SR*,3*SR*)-3,7-di-*t*-butyldimethylsilyloxy-2-methylheptanthioate **97**



General procedure D was followed with alcohol **89** (662 mg, 1.83 mmol) in DMF (1.5 ml), to which imidazole (498 mg, 7.32 mmol) and TBSCl (552 mg, 3.66 mmol) were added. Flash chromatography (2% EtOAc in hexane) gave a colourless oil **97** (861 mg, 99%). R_f (20% EtOAc in hexane) = 0.91; ν_{\max} (neat)/cm⁻¹ 1684 (C=O); ¹H NMR δ (250 MHz, CDCl₃) 3.99 (1H, m, CHOTBS), 3.58 (2H, t, $J = 6.0$ Hz, CH₂OTBS), 2.71 (1H, qd \equiv qn, $J = 6.8$ Hz, C(2)H), 1.58-1.30 (6H, m, 3 x CH₂), 1.43 (9H, s, *t*-BuS), 1.04 (3H, d, $J = 6.8$ Hz, C(2)CH₃), 0.87 (9H, s, *t*-BuSi), 0.86 (9H, s, *t*-BuSi), 0.02 (12H, s, 2 x SiMe₂); ¹³C NMR δ (50.3 MHz, CDCl₃) 202.7, 72.9, 63.0, 54.3, 47.6, 32.9, 32.4, 29.7 (3C), 25.8 (3C), 25.7 (3C), 20.3, 18.2, 17.9, 11.8, -4.6, -

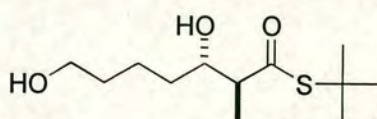
5.0, -5.5 (2C); **HRMS** (FAB, MeCN/thioglycerol) $[M+H]^+$ found 477.3261, $C_{24}H_{53}O_3SSi_2$ requires 477.3254; m/z 477 ($[M+H]^+$ 9), 331 (48), 149 (100%).

11 *t*-Butyl (2*SR*,3*SR*)-3-*t*-butyldimethylsilyloxy-7-hydroxy-2-methylheptanthioate 113



Thioester **97** (83 mg, 0.17 mmol) was dissolved in AcOH/THF/H₂O (3:1:1, 1 ml) and stirred at room temperature for 21 h. NaHCO₃ (5 ml; sat.) was added and the reaction extracted with EtOAc (3 x 5 ml), dried (MgSO₄) and the volatiles removed under reduced pressure. Flash chromatography (20% EtOAc in hexane) afforded the alcohol **113** as a clear, colourless oil (38 mg, 60%). R_f (20% EtOAc in hexane) = 0.31; ν_{max} (neat)/cm⁻¹ 3453 (OH), 1682 (C=O); 1H NMR δ (200 MHz, CDCl₃) 3.98-3.92 (3H, m, CH₂OH and OH), 3.61-3.55 (1H, m, CHOTBS), 2.67 (1H, qd=qn, J = 7.1 Hz, C(2)*H*), 1.65-1.30 (6H, m, 3 x CH₂), 1.39 (9H, s, *t*-BuS), 1.00 (3H, d, J = 7.1 Hz, C(2)CH₃), 0.82 (9H, s, *t*-BuSi), 0.02 (6H, s, 2 x Si(CH₃)₂).

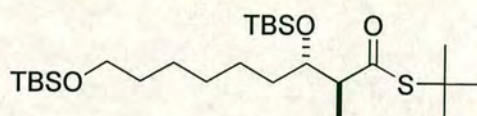
***t*-Butyl (2*SR*,3*SR*)-3,7-dihydroxy-2-methylheptanthioate 114**



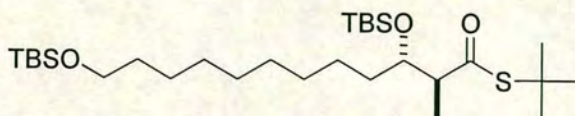
Thioester **97** (86 mg, 0.18 mmol) was dissolved in MeCN (2.5 ml) and HF (500 μ l; 40% aqueous) added. The reaction was stirred at room temperature for 50 min when deemed complete by tlc. Solid sodium bicarbonate was added until the effervescence ceased, the mixture passed through a small plug of MgSO₄ and extracted with EtOAc (3 x 5 ml). Flash chromatography (20% EtOAc in hexane) gave the diol **114** as a clear, colourless oil (37 mg, 84%). R_f (50% EtOAc in hexane) = 0.18; ν_{max}

(neat)/cm⁻¹ 3468 (OH), 1676 (C=O); ¹H NMR δ (200 MHz, CDCl₃) 3.64-3.58 (3H, m, CHOH and CH₂OH), 2.60 (1H, qd, *J* = 7.1 & 5.9 Hz, C(2)*H*), 2.36 (2H, br s, 2 x OH), 1.62-1.30 (6H, m, 3 x CH₂), 1.43 (9H, s, *t*-BuS), 1.18 (3H, d, *J* = 7.2 Hz, C(2)CH₃); ¹³C NMR δ (50.3 MHz, CDCl₃) 205.1, 73.6, 62.3, 53.6, 48.1, 34.2, 32.1, 29.5 (3C), 21.6, 14.8.

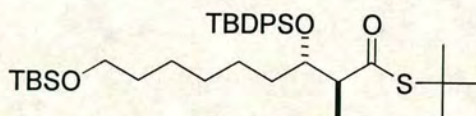
t*-Butyl (2*SR*,3*SR*)-3,9-di-*t*-butyldimethylsilyloxy-2-methylnonanthioate **98*



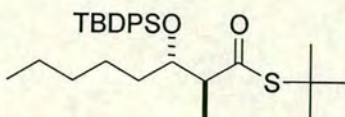
General procedure D was followed with alcohol **90** (3.48 g, 8.92 mmol) in DMF (10 ml), to which imidazole (2.43 g, 37.24 mmol) and TBSCl (2.69 g, 18.62 mmol) were added. Flash chromatography (5% EtOAc in hexane) gave a colourless oil **98** (4.23 g, 94%). *R*_f (20% EtOAc in hexane) = 0.91; *ν*_{max} (neat)/cm⁻¹ 1685 (C=O); ¹H NMR δ (250 MHz, CDCl₃) 4.00-3.95 (1H, m, CHOTBS), 3.58 (2H, t, *J* = 6.6 Hz, CH₂OTBS), 2.71 (1H, qd≡qn, *J* = 7.0 Hz, C(2)*H*), 1.58-1.28 (10H, m, 5 x CH₂), 1.43 (9H, s, *t*-BuS), 1.03 (3H, d, *J* = 7.0 Hz, C(2)CH₃), 0.88 (9H, s, *t*-BuSi), 0.86 (9H, s, *t*-BuSi), 0.04 (3H, s, SiMe), 0.03 (3H, s, SiMe), 0.03 (6H, s, 2 x SiMe); ¹³C NMR δ (50.3 MHz, CDCl₃) 202.8, 72.9, 63.1, 54.3, 47.6, 32.9, 32.5, 29.7 (3C), 29.5, 25.9 (3C), 25.8 (3C), 25.6, 23.9, 18.3, 17.9, 11.9, -4.6, -5.0, -5.4 (2C); HRMS (FAB, MeCN/thioglycerol) [M+H]⁺ found 505.3567, C₂₆H₅₇O₃SSi₂ requires 505.3586; *m/z* 505 ([M+H]⁺ 2), 415 (9), 359 (25).

***t*-Butyl (2*SR*,3*SR*)-3,12-di-*t*-butyldimethylsilyloxy-2-methyldodecanthioate 99**

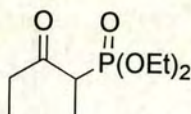
General procedure D was followed with alcohol **91** (1.92 g, 4.44 mmol) in DMF (5 ml), to which imidazole (1.21 g, 17.76 mmol) and TBSCl (1.34 g, 8.88 mmol) were added. The residue was passed through a small pad of silica eluting with 2% EtOAc in hexane to give **99** (2.12 g, 87%) which was used without further purification. R_f (10% EtOAc in hexane) = 0.77; ν_{\max} (neat)/ cm^{-1} 1682 (C=O); $^1\text{H NMR}$ δ (200 MHz, CDCl_3) 4.02-3.95 (1H, m, CHOTBS), 3.58 (2H, t, $J = 6.6$ Hz, CH_2OTBS), 2.71 (1H, qd=qn, $J = 7.0$ Hz, $\text{C}(2)\text{H}$), 1.58-1.28 (16H, m, 8 x CH_2), 1.43 (9H, s, *t*-BuS), 1.04 (3H, d, $J = 7.0$ Hz, $\text{C}(2)\text{CH}_3$), 0.88 (9H, s, *t*-BuSi), 0.86 (9H, s, *t*-BuSi), 0.03 (12H, s, 4 x SiMe); **HRMS** (CI, NH_3) $[\text{M}+\text{H}]^+$ found 547.4030, $\text{C}_{29}\text{H}_{63}\text{O}_3\text{SSi}_2$ requires 547.4030; m/z 547 ($[\text{M}+\text{H}]^+$ 100), 457 (42), 132 (52).

***t*-Butyl-(2*SR*,3*SR*)-9-*t*-butyldimethylsilyloxy-3-*t*-butyldiphenylsilyloxy-2-methylnonanthioate 100**

TBDPS protection of aldol product **90** was performed by Rachel Walker (TBDPSCl, imidazole, DMF, rt, 18h) to give protected adduct **100** in 81% yield.⁸⁸

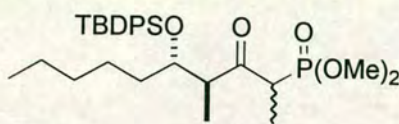
t*-Butyl (2*SR*,3*SR*)-3-*t*-butyldiphenylsilyloxy-2-methyloctanthioate **94*

TBDPS protection of the aldol product **94** was carried out by Dr. A. N. Hulme (TBSCl, imidazole, DMF, rt, 24 h) to give the protected aldol adduct **92** in 77% yield.⁸⁸

THIOESTER DISPLACEMENT**2-Diethoxyphosphorylpentan-3-one **96****

To a solution of diethyl ethanephosphonate (904 mg, 5.44 mmol) in THF (8 ml) was added ⁿBuLi (1.38 M solution in hexanes, 3.94 ml, 5.44 mmol) dropwise at -78 °C. After stirring for 50 min at -78 °C the light yellow solution was transferred *via* cannula into a solution of thioester **88** (199 mg, 1.36 mmol) in THF (15 ml) at -78 °C and the resulting solution was stirred for a further 50 min before carefully pouring onto NH₄Cl (30 ml, sat.). The mixture was extracted with CH₂Cl₂ (3 x 30 ml), washed with NaCl (60 ml, sat.), dried (MgSO₄) and the volatiles removed under reduced pressure. Flash chromatography (EtOAc) afforded **96** as a clear, colourless oil (193 mg, 73%). *R*_f (EtOAc) = 0.60; ν_{max} (neat)/cm⁻¹ 1713, 1250; ¹H NMR δ (200 MHz, CDCl₃) 4.20-3.95 (4H, m, P(OCH₂CH₃)₂), 3.19 (1H, dq, *J* = 24.9 & 7.0 Hz, CHP(O)), 2.80 (1H, dq, *J* = 18.5 & 7.3 Hz, CH₃CH_AH_B), 2.47 (1H, dq, *J* = 18.5 & 7.3 Hz, CH₃CH_AH_B), 1.32 (3H, dd, *J* = 18.3 & 7.0 Hz, CH(CH₃)P(O)), 1.28 (3H, t, *J* = 6.6 Hz), 1.02 (3H, t, *J* = 7.3 Hz, CH₃CH₂C(O)).

¹H NMR spectroscopic data in agreement with the literature.¹³⁹

(4*SR*,5*SR*)-5-*t*-Butyldiphenylsilyloxy-2-dimethoxyphosphoryl-4-methyldecan-3-one 95

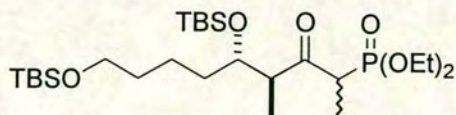
To a solution of dimethyl ethanephosphonate (192 mg, 1.39 mmol) in THF (5 ml) at -42 °C was added ^tBuLi (1.00 ml of a 1.7 M solution in hexanes, 1.7 mmol) dropwise. The yellow solution was stirred for 15 min and freshly distilled DMPU (195 mg, 1.50 mmol) added. After a further 10 min protected thioester **94** (90 mg, 0.19 mmol) was added, the solution cleared and was allowed to warm to room temperature over 4 h with stirring. The solution was poured onto NH₄Cl (20 ml, sat.) and the mixture was extracted with CH₂Cl₂ (3 x 20 ml). The organics were washed with NaCl (40 ml, sat.), dried (MgSO₄) and the volatiles removed under reduced pressure. Flash chromatography (50% EtOAc in hexane) afforded **95** as a clear, colourless oil (74mg, 73%). *R_f* (EtOAc) = 0.82; ν_{max} (neat)/cm⁻¹ 1705 (C=O) and 1260 (P=O); ¹H NMR δ (250 MHz, CDCl₃) ~3:1 mixture of diastereomers 7.69-7.31 (10H, m, 2 x Ph), 3.90-3.85 (1H, m, C(5)*H*), 3.70-3.59 (6H, m, P(OMe)₂), 3.12-2.81 (2H, m, C(4)*H* and C(2)*H*), 1.45-0.81 (23H, m, 4 x CH₂, C(2)CH₃, C(4)CH₃, *t*-BuSi), 0.72 (3H, t, *J* = 7.0 Hz, C(9)CH₃); HRMS (FAB, MeCN/thioglycerol) [M+H]⁺ found 533.2864, C₂₉H₄₆O₅PSi requires 533.2852; *m/z* 533 ([M+H]⁺ 5), 294 (31), 276 (20), 239 (54%).

General Procedure E: Thioester displacement

To a solution of diethyl ethanephosphonate (5.84 g, 35.11 mmol) in THF (20 ml) was added ⁿBuLi (1.54M solution in hexanes, 22.80 ml, 35.11 mmol) dropwise at -78 °C. After stirring for 50 min at -78 °C the light yellow solution was transferred *via* cannula into a solution of ester (7.98 mmol) in THF (15 ml) at -78 °C and the resulting solution was stirred for a further 50 min before carefully pouring onto NH₄Cl (150 ml, sat.). The mixture was extracted with CH₂Cl₂ (3 x 100 ml) washed with NaCl (200 ml, sat.), dried (MgSO₄) and the volatiles removed under reduced

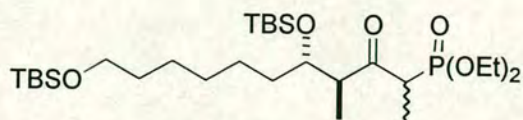
pressure. Purification of the crude material by flash chromatography (30 or 50% EtOAc in hexane) allowed the separation from any trace impurities.

(4*SR*,5*SR*)-5,9-Di-*t*-butyldimethylsilyloxy-2-diethoxyphosphoryl-4-methyl-nonan-3-one 101



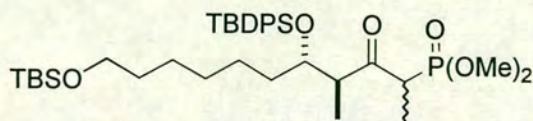
General Procedure E was followed with diethyl ethanephosphonate (585 mg, 3.52 mmol) and ⁿBuLi (1.32M solution in hexanes, 2.67 ml, 3.52 mmol) in THF (5 ml) which was added to thioester **97** (420 mg, 0.88 mmol) in THF (5 ml). Flash chromatography (50% EtOAc in hexane) afforded the phosphonate **101** as a clear, colourless oil (398 mg, 85%). *R*_f (50% EtOAc in hexane) = 0.59; *ν*_{max} (neat)/cm⁻¹ 1713, 1253; ¹H NMR δ (250 MHz, CDCl₃) ~3:1 mixture of diastereomers 4.28-4.08 (4H, m, P(OCH₂CH₃)₂), 4.02-3.96 (0.25H, m, CHOTBS), 3.95-3.85 (0.75H, m, CHOTBS), 3.62 (2H, t, *J* = 6.4 Hz, CH₂OTBS), 3.54-2.99 (2H, m, CHC(O) and CHP(O)), 1.65-1.25 (9H, m, 5 x CH₂, CH(CH₃)P(O)), 1.35 (6H, t, *J* = 7.1 Hz, 2 x CH₂CH₃), 1.15 (0.75H, d, *J* = 7.3 Hz, C(4)HCH₃), 1.02 (2.25H, d, *J* = 6.8 Hz, C(4)HCH₃), 0.92 (9H, s, *t*-BuSi), 0.90 (2.25H, s, *t*-BuSi), 0.88 (6.75H, s, *t*-BuSi), 0.07 (6H, s, SiMe), 0.07 (3.75H, SiMe), 0.00 (2.25H, SiMe); HRMS (FAB, MeCN/thioglycerol) [M+H]⁺ found, C₂₆H₅₇O₆Si₂P requires 552.3431.

(4*SR*,5*SR*)-5,11-Di-*t*-butyldimethylsilyloxy-2-diethoxyphosphoryl-4-methyl-undecan-3-one 102



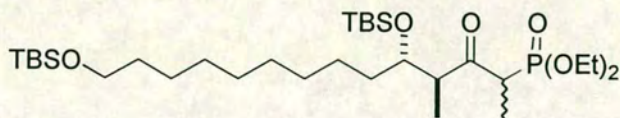
General Procedure E was followed with diethyl ethanephosphonate (5.84 g, 35.11 mmol) and ⁿBuLi (1.54M solution in hexanes, 22.80 ml, 35.11 mmol) in THF (20 ml) which was added to thioester **98** (4.02 g, 7.98 mmol) in THF (15 ml). Flash chromatography (50% EtOAc in hexane) afforded the phosphonate **102** as a clear, colourless oil (4.23 g, 94%). *R_f* (50% EtOAc in hexane) = 0.53; *ν*_{max} (neat)/cm⁻¹ 1712, 1251; ¹H NMR δ (250 MHz, CDCl₃) 3.3:1 mixture of diastereomers 4.26-4.06 (4H, m, P(OCH₂CH₃)₂), 4.02-3.95 (0.23H, m, CHOTBS), 3.94-3.84 (0.77H, m, CHOTBS), 3.63 (2H, t, *J* = 6.4 Hz, CH₂OTBS), 3.55-2.98 (2H, m, CHC(O) and CHP(O)), 1.65-1.20 (13H, m, 5 x CH₂, CH(CH₃)P(O)), 1.37 (6H, t, *J* = 7.1 Hz, 2 x CH₂CH₃), 1.15 (0.7H, d, *J* = 7.3 Hz, C(4)HCH₃), 1.02 (2.3H, d, *J* = 6.6 Hz, C(4)HCH₃), 0.93 (9H, s, *t*-BuSi), 0.90 (2.1H, s, *t*-BuSi), 0.89 (6.9H, s, *t*-BuSi), 0.08 (6H, s, SiMe), 0.07 (3.7H, SiMe), 0.00 (2.3H, SiMe); ¹³C NMR δ (62.9 MHz, CDCl₃) major diastereomer 209.1 (d, ²*J*_{P-C} = 3.6 Hz), 74.7, 63.07, 62.3 (2C, d, ²*J*_{P-C} = 6.7 Hz), 50.7, 48.2 (d, ¹*J*_{P-C} = 25.5 Hz), 33.4, 32.7, 29.6, 25.9 (3C), 25.8, 25.7 (3C), 22.8, 18.2, 17.8, 16.2 (2C), 12.4, 10.4 (d, ²*J*_{P-C} = 5.7 Hz), -4.5, -4.8, -5.4 (2C), minor diastereomer 208.9 (d, ²*J*_{P-C} = 4.5 Hz), 73.1, 63.14, 62.3 (2C, d, ²*J*_{P-C} = 6.7 Hz), 50.3, 45.0 (d, ¹*J*_{P-C} = 28.6 Hz), 33.4, 32.7, 29.6, 25.9 (3C), 25.8, 25.7 (3C), 24.5, 18.2, 17.9, 16.2 (2C), 12.3, 11.4 (d, ²*J*_{P-C} = 6.9 Hz), -4.7, -4.8, -5.4 (2C); HRMS (FAB, MeCN/thioglycerol) [M+H]⁺ found 580.3729, C₂₈H₆₂O₆Si₂P requires 580.3744; *m/z* 581 ([M+H]⁺ 24), 523 (100), 449 (78), 279 (99).

(4*SR*,5*SR*)-11-*t*-Butyldimethylsilyloxy-5-*t*-butyldiphenylsilyloxy-2-dimethoxyphosphoryl-4-methyl-undecan-3-one 104



To a solution of dimethylethanephosphonate (175 mg, 1.27 mmol) in THF (4 ml) to which was added *t*BuLi (0.88 ml of a 1.7 M solution, 1.49 mmol) dropwise. The yellow solution was stirred for 15 min and freshly distilled DMPU (65 mg, 0.51 mmol) added. After a further 10 min thioester **100** (130 mg, 0.21 mmol) was added, the solution cleared and was allowed to warm to room temperature over 2.5 h with stirring. The solution was poured onto NH₄Cl (20 ml, sat.) and the mixture was extracted with CH₂Cl₂ (3 x 20 ml). The organics were washed with NaCl (40 ml, sat.), dried (MgSO₄) and the volatiles removed under reduced pressure. Flash chromatography (50% EtOAc in hexane) afforded **104** as a clear, colourless oil (112 mg, 80%). *R_f* (50% EtOAc in hexane) = 0.38; ν_{max} (neat)/cm⁻¹ 1712 (C=O), 1253 (P=O), 1034 (P-O); ¹H NMR δ (250 MHz, CDCl₃) ~3:1 mixture of diastereomers 7.68-7.35 (10H, m, 2 x Ph), 3.93-3.86 (1H, m, CHOTBDPS), 3.71-3.60 (6H, m, P(OMe)₂), 3.50 (2H, t, *J* = 6.8 Hz, CH₂OTBS), 3.22-2.91 (2H, m, C(4)*H* and C(2)*H*), 1.45-0.85 (16H, m, 5 x CH₂ and 2 x CH₃), 1.02 (9H, s, *t*-BuSiPh₂), 0.87 (9H, s, *t*-BuSiMe₂), 0.01 (6H, s, SiMe₂); *m/z* (EI) 677 ([M+H]⁺ 2), 619 (15), 421 (25%).

(4*SR*,5*SR*)-5,14-Di-*t*-butyldimethylsilyloxy-2-diethoxyphosphoryl-4-methyl-tetradecan-3-one 103



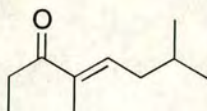
General Procedure E was followed with diethylethanephosponate (2.63 g, 15.80 mmol) and ⁿBuLi (1.59 M solution in hexanes, 9.95 ml, 15.80 mmol) in THF (20 ml) which was added to thioester **99** (1.96 g, 3.59 mmol) in THF (10 ml). Flash chromatography (30% EtOAc in hexane) afforded the phosphonate **103** as a clear, colourless oil (2.04 g, 94%). *R*_f (50% EtOAc in hexane) = 0.61; *ν*_{max} (neat)/cm⁻¹ 1711, 1254; ¹H NMR δ (200 MHz, CDCl₃) ~3:1 mixture of diastereomers 4.28-4.06 (4H, m, P(OCH₂CH₃)₂), 4.02-3.94 (0.25H, m, CHOTBS), 3.95-3.84 (0.75H, m, CHOTBS), 3.63 (2H, t, *J* = 6.6 Hz, CH₂OTBS), 3.55-2.98 (2H, m, CHC(O) and CHP(O)), 1.65-1.22 (9H, m, 5 x CH₂, CH(CH₃)P(O)), 1.35 (6H, t, *J* = 7.3 Hz, 2 x CH₂CH₃), 1.15 (0.75H, d, *J* = 7.0 Hz, C(4)HCH₃), 1.02 (2.25H, d, *J* = 7.0 Hz, C(4)HCH₃), 0.92 (9H, s, *t*-BuSi), 0.90 (2.25H, s, *t*-BuSi), 0.89 (6.75H, s, *t*-BuSi), 0.08 (6H, s, 2 x SiMe), 0.07 (3.75H, SiMe), 0.00 (2.25H, SiMe); HRMS (FAB, MeCN/thioglycerol) [M+H]⁺ found 623.4301, C₃₁H₆₈O₆Si₂P requires 623.4292; *m/z* 623 ([M+H]⁺ 44), 565 (70), 491 (64), 433 (9), 401 (34), 279 (100).

HORNER WADSWORTH EMMONS COUPLING

General procedure F: Horner-Wadsworth-Emmons coupling

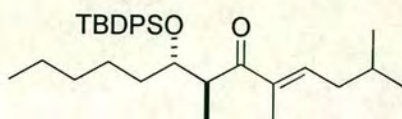
To a solution of β -ketophosphonate (0.70 mmol) in THF (5 ml) was added $\text{Ba}(\text{OH})_2 \cdot 8\text{H}_2\text{O}^\dagger$ (225 mg, 0.70 mmol) and the mixture stirred for 30 min until it became cloudy. Aldehyde (1.00 mmol) in THF:H₂O (40:1, 5 ml) was added and the reaction stirred at room temperature for 18 h, when deemed complete by tlc. The reaction mixture was diluted with CH_2Cl_2 (30 ml), washed with NaHCO_3 (30 ml; sat.), NaCl (30 ml; sat.), dried (MgSO_4) and the volatiles removed under reduced pressure. Flash chromatography (2 or 10% EtOAc in hexane) allowed separation of the *E*-alkene from any trace impurities.

(4*E*)-4,7-Dimethyloct-4-ene-3-one **105**

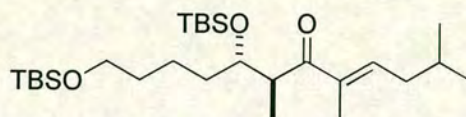


General procedure F was followed with phosphonate **96** (20 mg, 0.104 mmol) and $\text{Ba}(\text{OH})_2 \cdot 8\text{H}_2\text{O}$ (32 mg, 0.090 mmol) to which isovaleraldehyde (12 mg, 0.140 mmol) was added. Flash chromatography (10% EtOAc in hexane) afforded the *E*-alkene **105** as a clear, colourless oil (13 mg, 85%). Analysis of the 250 MHz ^1H NMR showed exclusive formation of the *E* isomer. R_f (20% EtOAc in hexane) = 0.62; ν_{max} (neat)/ cm^{-1} 1660 (C=O); ^1H NMR δ (250 MHz, CDCl_3) 6.63 (1H, t, J = 6.1 Hz, C(5)*H*), 2.68 (2H, q, J = 7.4 Hz, C(2)*H*₂), 2.10 (2H, dd \equiv t, J = J' = 6.7 Hz, C(6)*H*₂), 1.85-1.61 (1H, m, C(7)*H*), 1.75 (3H, d, J = 0.9 Hz, C(4)*CH*₃), 1.07 (3H, t, J = 7.4 Hz, C(1)*H*₃), 0.92 (6H, d, J = 6.7 Hz, C(8)*H*₃ and C(7)*CH*₃); ^{13}C NMR δ (50.3 MHz, CDCl_3) 202.6, 141.0, 137.4, 37.9, 30.2, 28.2, 22.3 (2C), 11.3, 8.7.

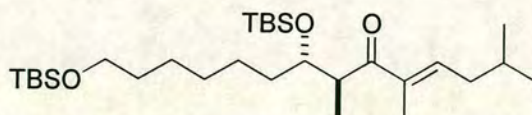
[†] The Barium Hydroxide was activated by heating in an oven at 120 °C for 2-12 h.

(4*E*,7*SR*,8*SR*)-8-*t*-Butyldiphenylsilyloxy-2,5,7-trimethyltridec-4-ene-6-one 106

General procedure F was used with β -ketophosphonate **95** (55 mg, 0.104 mmol) in THF/H₂O (40:1, 2 ml) with Ba(OH)₂•8H₂O (26 mg, 0.104 mmol) and isovaleraldehyde (8.9 mg, 0.104 mmol). The reaction was stirred for 22 h. Flash chromatography (2% EtOAc in hexane) afforded the alkene **106** as a clear, colourless oil (36mg, 71%). Analysis of the 250 MHz ¹H NMR showed exclusive formation of the *E* isomer. *R_f* (EtOAc) = 0.89; ν_{max} (neat)/cm⁻¹ 1663 (C=O); ¹H NMR δ (250MHz, CDCl₃) 7.71-7.25 (10H, m, 2 x Ph), 6.41 (1H, t, *J* = 6.4 Hz, C(4)*H*), 4.15-4.08 (1H, m, CHOTBDPS), 3.90 (1H, qd=qn, *J* = 6.8 Hz, CHC(O)), 2.03 (2H, dd, *J* = *J'* = 6.4 Hz, C(3)*H*₂), 1.68 (3H, s, C(5)CH₃), 1.46-0.91 (27H, m, 4 x CH₂, 3 x CH₃, CH(CH₃)₂ and *t*-BuSi), 0.75 (3H, t, *J* = 6.3 Hz, CH₃CH₂); ¹³C NMR δ (62.9 MHz, CDCl₃) 204.1 (CH), 141.2 (CH), 137.6 (C), 135.9 (2CH), 135.8 (2CH), 134.4 (C), 133.9 (C), 129.4 (CH), 129.3 (CH), 127.3 (2CH), 127.2 (2CH), 74.7 (CH), 44.5 (CH), 38.1 (CH₂), 32.7 (CH₂), 31.7 (CH₂), 28.2 (CH), 26.9 (3CH₃ and CH₂), 23.9 (CH₂), 22.5 (CH₃), 22.4 (CH₃), 19.3 (C), 13.9 (CH₃), 12.2 (CH₃), 11.8 (CH₃); HRMS (FAB, MeCN/thioglycerol) [M+H]⁺ found 492.3492, C₃₂H₄₉O₂Si requires 493.3502; *m/z* 493 ([M+H]⁺ 3), 435 (26), 199 (71), 137 (100%).

(4*E*,7*SR*,8*SR*)-8,12-Di-*t*-butyldimethylsilyloxy-2,5,7-trimethyldodec-4-en-6-one**107**

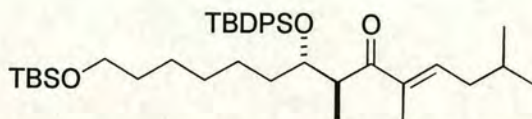
General procedure F was used with β -ketophosphonate **101** (380 mg, 0.690 mmol) in THF/H₂O (40:1, 10 ml) with Ba(OH)₂•8H₂O (225 mg, 0.700 mmol) and isovaleraldehyde (92 mg, 1.07 mmol). Flash chromatography (2% EtOAc in hexane) afforded the alkene **107** as a clear, colourless oil (316 mg, 94%). Analysis of the 200 MHz ¹H NMR showed exclusive formation of the *E* isomer. *R_f* (20% EtOAc in hexane) = 0.80; ν_{max} (neat)/cm⁻¹ 1664 (C=O); ¹H NMR δ (200 MHz, CDCl₃) 6.66 (1H, t, *J* = 6.8 Hz, C(4)*H*), 4.11-3.98 (1H, m, CHOTBS), 3.68 (2H, t, *J* = 6.2 Hz, CH₂OTBS), 3.52 (1H, dq \equiv qn, *J* = 7.3 Hz, C(7)*H*), 2.19 (2H, dd, *J* = *J*' = 6.8 Hz, C(3)*H*₂), 2.02-1.40 (7H, m, 3 x CH₂ and C(2)*H*), 1.81 (3H, s, C(5)CH₃), 1.16-0.84 (27H, m, 3 x CH₃ and 2 x *t*-BuSi), 0.08 (3H, s, SiMe); 0.00 (3H, s, SiMe); ¹³C NMR δ (62.9 MHz, CDCl₃) 204.9 (C), 141.6 (CH), 137.8 (C), 73.6 (CH), 62.9 (CH₂), 43.8 (CH), 38.1 (CH₂), 32.9 (2CH₂), 28.2 (CH), 25.6 (6CH₃), 22.4 (2CH₃), 19.5 (CH₂), 17.8 (2C), 13.3 (CH₃), 11.7 (CH₃), -4.7 (2CH₃), -5.0 (2CH₃); **HRMS** (FAB, MeCN/thioglycerol) [M+H]⁺ found 485.3841, C₂₇H₅₇O₃Si₂ requires 485.3844; *m/z* 485 ([M+H]⁺ 12), 427 (54), 331 (62%).

(4*E*,7*SR*,8*SR*)-8,14-Di-*t*-butyldimethylsilyloxy-2,5,7-trimethyltetradec-4-en-6-one 108

General procedure F was used with β -ketophosphonate **102** (4.05 g, 7.59 mmol) in THF (100 ml) with Ba(OH)₂•8H₂O (2.30 g, 7.30 mmol) and isovaleraldehyde (879

mg, 10.02 mmol) in THF/H₂O (40:1, 100 ml). Flash chromatography (2% EtOAc in hexane) afforded the alkene **108** as a clear, colourless oil (3.11 g, 85%). Analysis of the 250 MHz ¹H NMR showed exclusive formation of the *E* isomer. *R_f* (20% EtOAc in hexane) = 0.84; ν_{max} (neat)/cm⁻¹ 1660 cm⁻¹(C=O); ¹H NMR δ (250 MHz, CDCl₃) 6.65 (1H, t, *J* = 6.6 Hz, C(4)*H*), 3.97-3.92 (1H, m, *CHOTBS*), 3.57 (2H, t, *J* = 6.5 Hz, *CH₂OTBS*), 3.42 (1H, dq=qn, *J* = 6.9 Hz, C(7)*H*), 2.11 (2H, dd, *J* = *J'* = 6.6 Hz, C(3)*H₂*), 1.82-1.61 (1H, m, C(2)*H*), 1.73 (3H, s, C(5)*CH₃*), 1.54-1.26 (10H, m, 5 x *CH₂*), 0.94 (3H, d, *J* = 6.6 Hz, *CH(CH₃)_A(CH₃)_B*), 0.93 (3H, d, *J* = 6.6 Hz, *CH(CH₃)_A(CH₃)_B*)^o, 0.91 (3H, d, *J* = 6.9 Hz, C(7)*H(CH₃)*), 0.86 (9H, s, *t*-BuSi), 0.78 (9H, s, *t*-BuSi), 0.02 (6H, s, SiMe₂), -0.02 (3H, s, SiMe), -0.10 (3H, s, SiMe); ¹H NMR assignments were confirmed on the basis of ¹H/¹³C correlation at 200 MHz; ¹³C NMR δ (62.9 MHz, CDCl₃) 204.9, 141.4, 137.9, 73.8, 63.1, 43.8, 38.1, 33.1, 32.7, 29.6, 28.3, 25.8 (3C), 25.7 (4C), 23.3, 22.4 (2C), 17.8 (2C), 13.3, 11.7, -4.7, -5.0, -5.4 (2C); HRMS (CI, NH₃) [*M*+*H*]⁺ found 513.4160, C₂₉H₆₁O₃Si₂ requires 513.4159; *m/z* 513 ([*M*+*H*]⁺ 50), 387 (10), 383 (75), 245 (27), 132 (68%).

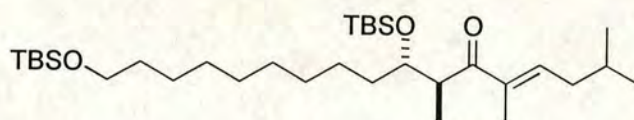
(4*E*,7*SR*,8*SR*)-14-*t*-Butyldimethylsilyloxy-8-*t*-butyldiphenylsilyloxy-2,5,7-trimethyltetradec-4-en-6-one **110**



General procedure F was used with β -ketophosphonate **94** (112 mg, 0.169 mmol) in THF (10 ml) with Ba(OH)₂•8H₂O (54 mg, 0.169 mmol) and isovaleraldehyde (15 mg, 0.174 mmol) in THF/H₂O (40:1, 10 ml). Flash chromatography (2% EtOAc in hexane) afforded the product **110** as a clear, colourless oil (88 mg, 82%). Analysis of the 360 MHz ¹H NMR showed exclusive formation of the *E* isomer. *R_f* (20% EtOAc in hexane) = 0.80; ν_{max} (neat)/cm⁻¹ 1664 (C=O); ¹H NMR δ (360 MHz, CDCl₃) 7.69-7.31 (10H, m, Ar), 6.45-6.39 (1H, t, *J* = 6.9 Hz, C(4)*H*), 4.12 (1H, td, *J* = 6.2 & 2.8 Hz, *CHOTBDPS*), 3.52-3.43 (3H, m, *CH₂OTBS* and C(7)*H*), 2.04 (2H, t, *J* = 6.9 Hz, C(3)*H₂*), 1.68 (3H, br s, C(5)*CH₃*), 1.42-0.71 (20H, m, 5 x *CH₂*, C(2)*H*, 3 x

CH_3), 0.99 (9H, s, *t*-BuSiPh₂), 0.89 (9H, s, *t*-BuSiMe₂), 0.03 (6H, s, SiMe₂); ¹H NMR decoupling experiments δ (250 MHz, CDCl₃) Irradiation at 6.42 led to simplification at 2.04 and 1.68, irradiation at 4.12 led to simplification at 3.52-3.43, irradiation at 3.50 led to simplification at 4.12 and irradiation at 2.04 caused simplification at 6.42; ¹³C NMR δ (62.9 MHz, CDCl₃) 204.1 (C), 141.3 (CH), 137.6 (C), 135.9 (2CH), 135.8 (2CH), 134.4 (C), 133.9 (C), 129.4 (CH), 129.3 (CH), 127.3 (2CH), 127.2 (2CH), 74.7 (CH), 63.2 (CH₂), 44.4 (CH), 38.1 (CH₂), 32.7 (2CH₂), 29.3 (CH₂), 28.2 (CH), 26.9 (3CH₃), 25.9 (3CH₃), 25.6 (CH₂), 24.2 (CH₂), 22.5 (CH₃), 22.4 (CH₃), 19.3 (C), 18.3 (C), 12.2 (CH₃), 11.8 (CH₃), -5.3 (2CH₃); HRMS (FAB, MeCN/thioglycerol) [M+H]⁺ found 637.4497, C₃₉H₆₅O₃Si₂ requires 637.4472; *m/z* 637 ([M+H]⁺ 4), 580 (27), 331 (100%).

(4*E*,7*SR*,8*SR*)-8,17-Di-*t*-butyldimethylsilyloxy-2,5,7-trimethylheptadec-4-en-6-one 109



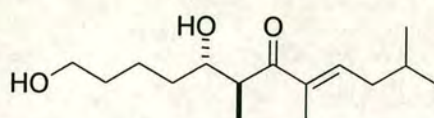
General procedure F was used with β -ketophosphonate **103** (2.04 g, 3.27 mmol) in THF (30 ml) with Ba(OH)₂•8H₂O (848 mg, 2.70 mmol) and isovaleraldehyde (435 mg, 5.06 mmol) in THF/H₂O (40:1, 30 ml). Flash chromatography (2% EtOAc in hexane) afforded the product **109** as a clear, colourless oil (1.65 g, 85%). Analysis of the 250 MHz ¹H NMR showed exclusive formation of the *E* isomer. *R_f* (20% EtOAc in hexane) = 0.86; ν_{max} (neat)/cm⁻¹ 1666 (C=O); ¹H NMR δ (250 MHz, CDCl₃) 6.74 (1H, br t, *J* = 6.8 Hz, C(4)*H*), 4.15-4.00 (1H, m, CHOTBS), 3.67 (2H, t, *J* = 6.3 Hz, CH₂OTBS), 3.50 (1H, dq=qn, *J* = 7.0 Hz, C(7)*H*), 2.20 (2H, dd, *J* = *J'* = 7.0 Hz, C(3)*H*₂), 1.96-1.72 (1H, m, C(2)*H*), 1.93 (3H, br s, C(5)CH₃), 1.62-1.30 (16H, m, 8 x CH₂), 1.02 (6H, d, *J* = 6.6 Hz, C(2)H(CH₃)₂), 1.01 (3H, d, *J* = 7.0 Hz, C(7)HCH₃), 0.96 (9H, s, *t*-BuSi), 0.88 (9H, s, *t*-BuSi), 0.12 (6H, s, SiMe₂), 0.08 (3H, s, SiMe), 0.00 (3H, s, SiMe); ¹³C NMR δ (62.9 MHz, CDCl₃) 205.0, 141.4, 137.9, 73.8, 63.2, 43.9, 38.1, 33.1, 32.8, 29.8, 29.5 (2C), 29.3, 28.3, 25.9 (3C), 25.7 (4C), 23.3, 22.5

(2C), 18.3, 17.9, 13.3, 11.8, -4.7, -5.0, -5.4 (2C); m/z (Electrospray) 603 (M^+ 100), 449 (53), 225 (15%). **NOE EXPERIMENTS:** See Section 2.4.2.

General procedure G: Desilylation of HWE products

To a solution of the HWE adduct (0.60 mmol) in acetonitrile (13 ml) and THF (4 ml) was added HF (1.90 ml; 40% aqueous). The reaction was stirred at room temperature for 50 min monitoring constantly^Y when deemed complete by tlc. Solid sodium bicarbonate was added until the effervescence ceased. H₂O (20 ml) was added carefully and the mixture extracted with EtOAc (3 x 30 ml). The extracts were washed with NaHCO₃ (40 ml; sat.), NaCl (40 ml; sat.), dried (MgSO₄) and the volatiles removed under reduced pressure. Flash chromatography (50% EtOAc in hexane) allowed the separation from any minor impurities.

(4E,7SR,8SR)-8,12-Dihydroxy-2,5,7-trimethyldodec-4-en-6-one 115

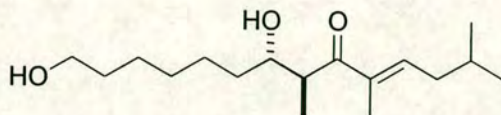


General procedure G was followed with HWE adduct **107** (314 mg, 0.65 mmol) in acetonitrile (15 ml) and THF (5 ml) to which was added HF (1.90 ml; 40% aqueous). Flash chromatography (50% EtOAc in hexane) afforded the diol **115** as a clear, colourless oil (145 mg, 87%). R_f (50% EtOAc in hexane) = 0.28; ν_{\max} (neat)/cm⁻¹ 3393 (OH), 1647 (C=O); ¹H NMR δ (200 MHz, CDCl₃) 6.66 (1H, t, J = 7.1 Hz, C(4)H), 3.78-3.50 (3H, m, CHOH and CH₂OH), 3.27 (1H, dq=qn, J = 7.3 Hz, C(7)H), 2.79 (1H, br, s, OH), 2.19 (2H, dd, J = J' = 7.1 Hz, C(3)H₂), 1.81-1.60 (1H, m, C(2)H), 1.73 (3H, s, C(5)CH₃), 1.63-1.28 (6H, m, 3 x CH₂), 1.10 (3H, d, J = 7.3 Hz, C(7)CH₃), 0.93 (6H, d, J = 6.6 Hz, C(2)H(CH₃)₂); ¹³C NMR δ (62.9 MHz, CDCl₃) 207.4 (C), 143.0 (CH), 137.3 (C), 73.9 (CH), 62.3 (CH₂), 43.7 (CH), 38.1 (CH₂), 34.4 (CH₂), 32.3 (CH₂), 28.2 (CH), 22.4 (CH₃), 22.3 (CH₃), 21.9 (CH₂), 16.0

^Y Longer reaction times and/or improper quenching of the reaction allowed the formation of a HiR_f non-uv active spot caused by HF addition to the unsaturated ketone.

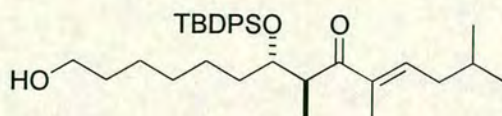
(CH₃), 11.3; **HRMS** (FAB, MeCN/thioglycerol) [M+H]⁺ found 257.2113, C₁₅H₂₉O₃ requires 257.2117 **m/z** 257 ([M+H]⁺ 2), 183 (20), 125 (50%).

(4*E*,7*SR*,8*SR*)-8,14-Dihydroxy-2,5,7-trimethyltetradec-4-en-6-one 116



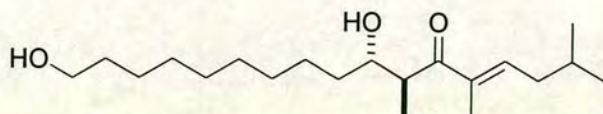
General procedure G was followed with HWE adduct **108** (1.27 g, 2.47 mmol) in acetonitrile (40 ml) and THF (10 ml) to which was added HF (7.10 ml; 40% aqueous). Flash chromatography (50% EtOAc in hexane) afforded diol **116** as a clear, colourless oil (630 mg, 90%). **R_f** (50% EtOAc in hexane) = 0.41; ν_{\max} (neat)/cm⁻¹ 3407 (OH), 1656 (C=O); ¹H NMR δ (200 MHz, CDCl₃) 6.66 (1H, t, *J* = 6.6 Hz, C(4)*H*), 3.72-3.60 (1H, m, CHOH), 3.57 (2H, t, *J* = 6.6 Hz, CH₂OH), 3.26 (1H, dq, *J* = 7.1 and 7.0 Hz, C(7)*H*), 3.10 (1H, br d, *J* = 6.1 Hz, C(8)HOH), 2.79 (1H, br, s, OH), 2.13 (2H, dd, *J* = *J'* = 6.6 Hz, C(3)*H*₂), 1.81-1.60 (1H, m, C(2)*H*), 1.74 (3H, s, C(5)*H*₃), 1.65-1.20 (10H, m, 5 x CH₂), 1.13 (3H, d, *J* = 7.2 Hz, C(7)CH₃), 0.93 (6H, d, *J* = 6.6 Hz, C(2)H(CH₃)₂); ¹³C NMR δ (50.3 MHz, CDCl₃) 207.6, 143.0, 137.5, 74.1, 62.7, 43.6, 38.1, 34.9, 32.5, 29.1, 28.2, 25.7, 25.5, 22.3 (2C), 16.0, 11.2; **HRMS** (CI, NH₃) [M+H]⁺ found 285.2430, C₁₇H₃₃O₃ requires 285.2430; **m/z** 285 ([M+H]⁺ 5), 172 (57), 155 (100), 148 (32%); **Analysis** found %C, 71.58; %H, 11.56; C₁₇H₃₂O₃ requires %C, 71.79; %H, 11.34.

(4*E*,7*SR*,8*SR*)-8-*t*-Butyldiphenylsilyloxy-14-hydroxy-2,5,7-trimethyltetradec-4-en-6-one 119



Protected alcohol **110** (88 mg, 0.138 mmol) was dissolved in AcOH/THF/H₂O (3:1:1, 2.5 ml) and stirred at room temperature for 4 h. NaHCO₃ (5 ml; sat.) was added, the reaction extracted with EtOAc (3 x 5 ml), dried (MgSO₄) and the volatiles removed under reduced pressure. Flash chromatography (2-10% EtOAc in hexane) afforded the alcohol **119** as a clear, colourless oil (60 mg, 84%). *R_f* (20% EtOAc in hexane) = 0.22; ν_{max} (neat)/cm⁻¹ 3390 (OH), 1662 (C=O); ¹H NMR δ (200 MHz, CDCl₃) 7.69-7.29 (10H, m, Ar), 6.41 (1H, t, *J* = 6.3 Hz, C(4)*H*), 4.11 (1H, m, CHOTBDPS), 3.55 (2H, t, *J* = 6.6 Hz, CH₂OH), 3.48 (1H, m, C(7)*H*), 3.30 (1H, br s, OH), 2.04 (2H, t, *J* = 6.6 Hz, C(3)*H*₂), 1.80-1.63 (1H, m, C(2)*H*), 1.71 (3H, s, C(5)CH₃), 1.44-0.86 (10H, m, 5 x CH₂), 0.98 (3H, d, *J* = 7.2 Hz, C(7)CH₃), 0.98 (9H, s, *t*-BuSiPh₂), 0.93 (6H, d, *J* = 6.6 Hz, C(2)H(CH₃)₂); ¹³C NMR δ (62.9 MHz, CDCl₃) 204.2 (C), 141.4 (CH), 137.5 (C), 135.9 (2CH), 135.8 (2CH), 134.4 (C), 133.9 (C), 129.4 (CH), 129.3 (CH), 127.3 (2CH), 127.2 (2CH), 74.6 (CH), 62.8 (CH₂), 44.4 (CH), 38.1 (CH₂), 32.6 (CH₂), 32.5 (CH₂), 29.1 (CH₂), 28.2 (CH), 26.8 (3CH₃), 25.4 (CH₂), 24.2 (CH₂), 22.5 (CH₃), 22.4 (CH₃), 19.3 (C), 12.2 (CH₃), 11.8 (CH₃); HRMS (FAB, MeCN/thioglycerol) [M+H]⁺ found 523.3610, C₃₃H₅₁O₃Si requires 523.3607; *m/z* 523 ([M+H]⁺ 31), 445 (44), 183 (100%).

(4*E*,7*SR*,8*SR*)-8,14-Dihydroxy-2,5,7-trimethylheptadec-4-en-6-one 117



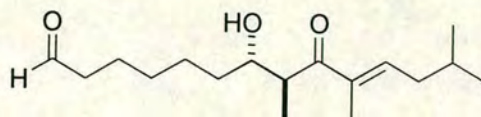
General procedure G was followed with HWE adduct **109** (172 mg, 0.310 mmol) in acetonitrile (6 ml) and THF (2 ml) to which was added HF (1.5 ml; 40% aqueous).

Flash chromatography (50% EtOAc in hexane) afforded a clear, colourless oil **117** (89 mg, 88%). R_f (50% EtOAc in hexane) = 0.41; ν_{\max} (neat)/ cm^{-1} 3407 (OH), 1652 (C=O); $^1\text{H NMR}$ δ (200 MHz, CDCl_3) 6.66 (1H, t, $J = 7.3$ Hz, C(4)H), 3.72-3.54 (1H, m, CHOH), 3.58 (2H, t, $J = 6.6$ Hz, CH_2OH), 3.27 (1H, dq, $J = 7.3$ & 6.7 Hz, C(7)H), 3.14 (1H, br s, OH), 2.13 (2H, dd, $J = J' = 7.0$ Hz, C(3)H₂), 1.95 (1H, br s, OH), 1.86-1.64 (1H, m, C(2)H), 1.73 (3H, s, C(5)CH₃), 1.59-1.18 (16H, m, 8 x CH₂), 1.12 (3H, d, $J = 7.3$ Hz, C(7)CH₃), 0.91 (6H, d, $J = 6.6$ Hz, C(2)H(CH₃)₂); $^{13}\text{C NMR}$ δ (50.3 MHz, CDCl_3) 207.7, 143.0, 137.5, 74.2, 62.7, 43.5, 38.0, 35.0, 32.5, 29.3 (2C), 29.2 (2C), 28.2, 25.7, 25.5, 22.3 (2C), 16.0, 11.2; **HRMS** (FAB, MeCN/thioglycerol) $[\text{M}+\text{H}]^+$ found 327.2900, $\text{C}_{20}\text{H}_{39}\text{O}_3$ requires 327.2899; m/z 327 ($[\text{M}+\text{H}]^+$ 2), 125 (82), 43 (100%).

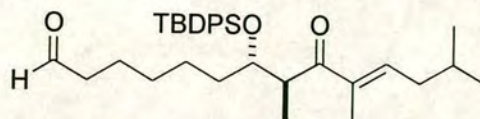
General Procedure H: Selective TEMPO oxidation of diols

To a vigorously stirred mixture of diol (0.20 mmol), TEMPO (0.4 mg, 2.0 μmol), tetra-*n*-butylammonium chloride (2.8 mg, 0.01 mmol), sodium bromide (2.1 mg, 0.02 mmol), CH_2Cl_2 (1 ml) and NaHCO_3 (1 ml; sat.) was added a mixture of NaOCl (293 μl of a 1.04 M aqueous solution, 0.30 mmol) in NaHCO_3 (0.2 ml; sat.) and NaCl (0.4 ml; sat.) dropwise. The solution became a red colour, turning yellow and finally colourless as the reaction progressed. The two layers were separated and the aqueous phase extracted with CH_2Cl_2 (2 x 3 ml). The organic phases were combined, washed with NaHCO_3 (5 ml; sat.), NaCl (5 ml; sat.), dried (MgSO_4) and the volatiles removed under reduced pressure to give a yellow oil. Flash chromatography (30 or 40% EtOAc in hexane) through a very short plug of silica allowed isolation of the aldehyde as an unstable[§] clear oil.

[§] It was noted that the aldehyde was less labile before purification and that residual TEMPO was thought to stabilise the oxidised product.⁹⁵

(7*SR*,8*SR*,10*E*)-7-Hydroxy-9-oxo-8,10,13-trimethyltetradec-10-enal 123

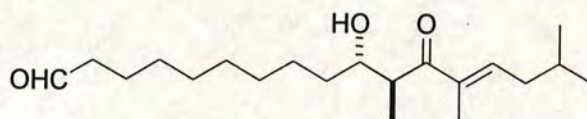
General procedure H was followed with diol **116** (156 mg, 0.556 mmol), TEMPO (0.9 mg, 5.56 μ mol), tetra-*n*-butylammonium chloride (7.7 mg, 0.03 mmol), sodium bromide (5.7 mg, 0.06 mmol), CH_2Cl_2 (4 ml) and NaHCO_3 (2 ml; sat.) to which was added NaOCl (944 μ l of a 1.06 M aqueous solution, 1.00 mmol) in NaHCO_3 (0.4 ml; sat.) and NaCl (0.8 ml; sat.). Flash chromatography (30% EtOAc in hexane) afforded a clear yellow unstable oil **123** (150 mg, 95%). R_f (50% EtOAc in hexane) = 0.58; ν_{max} (neat)/ cm^{-1} 3456 (OH), 2680 (CH, aldehyde), 1722 (C=O, aldehyde), 1655 (C=O, enone); ^1H NMR δ (200 MHz, CDCl_3) 9.69 (1H, t, J = 0.7 Hz, $\text{HC}=\text{O}$), 6.62 (1H, t, J = 7.2 Hz, C(11) H), 3.74-3.52 (1H, m, CHOH), 3.29-3.15 (1H, m, C(8) H), 3.07 (1H, br s, OH), 2.36 (2H, td, J = 7.3 & 0.7 Hz, $\text{HC}=\text{OCH}_2$), 2.10 (2H, dd \equiv t, J = 7.2 Hz, C(12) H_2), 1.82-1.20 (9H, m, 4 \times CH_2 and C(13) H), 1.70 (3H, s, C(10) CH_3), 1.09 (3H, d, J = 7.3 Hz, C(8) HCH_3), 0.88 (6H, d, J = 6.6 Hz, C(13) $\text{H}(\text{CH}_3)_2$); ^{13}C NMR δ (50.3 MHz, CDCl_3) 206.4, 201.7, 141.9, 136.4, 72.9, 42.6 (2C), 37.0, 33.6, 27.8, 27.1, 24.4, 21.2 (2C), 20.7, 14.8, 10.2.

(7*SR*,8*SR*,10*E*)-7-*t*-Butyldiphenylsilyloxy-9-oxo-8,10,13-trimethyltetradec-10-enal 120

General procedure B was followed for alcohol **119** (36 mg, 0.069 mmol) and IBX (56 mg, 0.20 mmol) in DMSO (0.40 ml) and THF (0.20 ml) and stirred for 3 h. Flash chromatography (EtOAc) gave aldehyde **120** as a clear, colourless oil (34 mg, 95%). R_f (20% EtOAc in hexane) = 0.48; ν_{max} (neat)/ cm^{-1} 1725 (C=O, aldehyde), 1662

(C=O, enone); ^1H NMR δ (250 MHz, CDCl_3) 9.66 (1H, t, $J = 1.8$ Hz, HC=O), 7.68-7.30 (10H, m, Ar), 6.45-6.39 (1H, t, $J = 6.3$ Hz, C(11) H), 4.16-4.08 (1H, m, CHOTBDPS), 3.52-3.46 (1H, qd \equiv qn, $J = 6.8$ Hz, C(8) H), 2.23 (2H, td, $J = 7.3$ & 1.8 Hz, C(2) H_2), 2.04 (2H, t, $J = 6.3$ Hz, C(12) H_2), 1.68 (3H, s, C(10) H_3), 1.59-0.86 (18H, m, 4 x CH_2 , C(13) H , 3 x CH_3), 0.98 (9H, s, $t\text{-BuSiPh}_2$); ^{13}C NMR δ (62.9 MHz, CDCl_3) 204.0 (C), 202.7 (C), 141.4 (CH), 137.5 (C), 135.9 (2CH), 135.8 (2CH), 134.4 (C), 133.8 (C), 129.4 (CH), 129.3 (CH), 127.3 (2CH), 127.2 (2CH), 74.5 (CH), 44.4 (CH), 43.6 (CH_2), 38.1 (CH_2), 32.4 (CH_2), 28.8 (CH_2), 28.2 (CH), 26.8 (3 CH_3), 24.0 (CH_2), 22.4 (CH_3), 22.3 (CH_3), 21.7 (CH_2), 19.3 (C), 12.2 (CH_3), 11.7 (CH_3); HRMS (FAB, MeCN /thioglycerol) $[\text{M}+\text{H}]^+$ found 521.3451, $\text{C}_{33}\text{H}_{49}\text{O}_3\text{Si}$ requires 521.3465; m/z 521 ($[\text{M}+\text{H}]^+$ 9), 463 (60), 135 (100%).

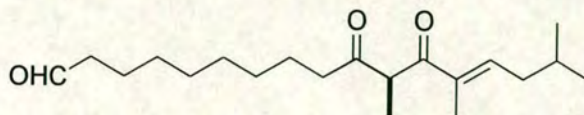
(10*SR*,11*SR*,13*E*)-10-Hydroxy-12-oxo-11,13,16-trimethylheptadec-13-enal 124



General procedure H was followed with diol **117** (100 mg, 0.556 mmol), TEMPO (0.5 mg, 3.2 μmol), tetra-*n*-butylammonium chloride (4.0 mg, 15 μmol), sodium bromide (3 mg, 0.03 mmol), CH_2Cl_2 (2 ml) and NaHCO_3 (1 ml; sat.) to which was added NaOCl (384 μl of a 1.12 M aqueous solution, 1.00 mmol) in NaHCO_3 (0.3 ml; sat.) and NaCl (0.6 ml; sat.). Flash chromatography (30% EtOAc in hexane) afforded aldehyde **124** as a clear, unstable oil (82 mg, 83%). R_f (50% EtOAc in hexane) = 0.75; ν_{max} (neat)/ cm^{-1} 1727 (C=O, aldehyde), 1663 (C=O, enone); ^1H NMR δ (200 MHz, CDCl_3) 9.69 (1H, t, $J = 1.9$ Hz, HC=O), 6.66 (1H, t, $J = 7.2$ Hz, C(14) H), 3.76-3.58 (1H, m, C(10) HOH), 3.27 (1H, qd \equiv qn, $J = 7.0$ Hz, C(11) H), 3.04 (1H, br d, $J = 7.3$ Hz, OH), 2.38 (2H, td, $J = 7.3$ & 1.9 Hz, HC=OCH_2), 2.13 (2H, dd \equiv t, $J = 7.2$ Hz, C(15) H_2), 1.87-1.18 (15H, m, 7 x CH_2 and C(16) H), 1.74 (3H, s, C(13) CH_3), 1.13 (3H, d, $J = 7.0$ Hz, C(11) HCH_3), 0.91 (6H, d, $J = 6.6$ Hz, C(16) $\text{H}(\text{CH}_3)_2$); ^{13}C NMR δ (50.3 MHz, CDCl_3) 207.7, 202.9, 142.9, 137.5, 74.2, 43.7, 43.5, 38.1, 35.0, 29.3, 29.2, 29.1, 28.9, 28.2, 25.7, 22.3 (2C), 21.8, 16.1, 11.3.

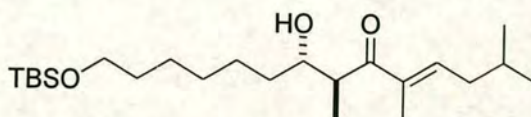
In an earlier attempt at the oxidation with 1 equivalent of IBX a mixture of the above aldehyde **124** and the doubly oxidised product **121** were observed.

(11*SR*,13*E*)-10,12-Dioxo-11,13,16-trimethylheptadec-13-enal **121**



R_f (20% EtOAc in hexane) = 0.49; $^1\text{H NMR}$ δ (200 MHz, CDCl_3) 9.74 (1H, t, J = 1.6 Hz, $\text{HC}=\text{O}$), 6.68 (1H, t, J = 7.1 Hz, C(14) H), 4.21 (1H, q, J = 7.0 Hz, C(11) H), 3.27 (1H, qd \equiv qn, J = 7.0 Hz, C(11) H), 2.46 (4H, m, $\text{HC}=\text{OC}(2)\text{H}_2$ and C(9) $\text{H}_2\text{C}=\text{O}$), 2.14 (2H, dd \equiv t, J = 7.1 Hz, C(15) H_2), 1.88-1.15 (15H, m, 7 \times CH_2 and C(16) H), 1.77 (3H, s, C(13) CH_3), 1.25 (3H, d, J = 7.0 Hz, C(11) HCH_3), 0.91 (6H, d, J = 6.6 Hz, C(16) $\text{H}(\text{CH}_3)_2$); $^{13}\text{C NMR}$ δ (50.3 MHz, CDCl_3) 207.6, 202.9, 198.6, 143.9, 137.4, 54.9, 43.7, 39.8, 38.1, 28.9 (3C), 28.8, 28.2, 23.3, 22.3 (2C), 21.8, 16.1, 11.5.

(4*E*,7*SR*,8*SR*)-14-*t*-Butyldimethylsilyloxy-8-hydroxy-2,5,7-trimethyltetradec-4-en-6-one **125**



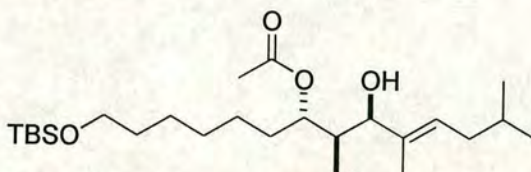
To a solution of diol **116** (87 mg, 0.31 mmol) in DMF (0.5 ml) was added imidazole (38 mg, 0.55 mmol) and TBSCl (61 mg, 0.40 mmol) and the reaction stirred at room temperature for 4.5h when deemed complete by tlc. The reaction was quenched by the addition of NaCl (2 ml; sat.) and the mixture extracted with EtOAc (3 \times 3 ml). The combined organic extracts were washed with a further portion of NaCl (10 ml; sat.), dried (MgSO_4) and the volatiles removed under reduced pressure. Flash chromatography (5-15% EtOAc in hexane) afforded the monoprotected diol **125** as a clear, colourless oil (104 mg, 85%). R_f (50% EtOAc in hexane) = 0.72; ν_{max}

(neat)/cm⁻¹ 3395 (OH), 1648 (C=O); ¹H NMR δ (200 MHz, CDCl₃) 6.65 (1H, t, J = 7.3 Hz, C(4)*H*), 3.72-3.58 (1H, m, C(8)*HOH*), 3.56 (2H, t, J = 6.4 Hz, CH₂OTBS), 3.26 (1H, qd=qn, J = 7.0 Hz, C(7)*H*), 3.00 (1H, d, J = 7.3 Hz, OH), 2.13 (2H, dd=t, J = 7.3 Hz, C(3)*H*₂), 1.86-1.18 (11H, m, 5 x CH₂ and C(2)*H*), 1.74 (3H, s, C(5)CH₃), 1.12 (3H, d, J = 7.0 Hz, C(7)HCH₃), 0.91 (6H, d, J = 6.6 Hz, C(2)H(CH₃)₂), 0.85 (9H, s, *t*-BuSi), 0.00 (6H, s, SiMe₂).

Samarium (II) Iodide

A suspension of iodine (259 mg, 1.0 mmol) and samarium (207 mg, 1.40 mmol, ~40 mesh) in THF (10 ml) was heated under reflux in the absence of light (this is not critical but SmI₂ is known to be light sensitive and should be treated accordingly) for 1 h after which time a deep blue solution of SmI₂ (0.1 M in THF) has formed. The solution was then cooled to room temperature where it could be stored under Ar for a few hours before oxidation to a yellow Sm (III) species occurred.

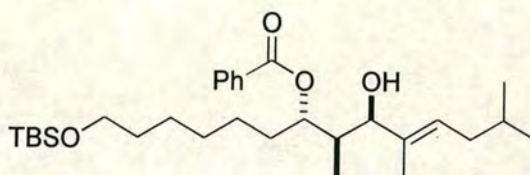
(4*E*,6*RS*,7*SR*,8*SR*)-8-Ethanoyloxy-14-*t*-butyldimethylsilyloxy-6-hydroxy-2,5,7-trimethyltetradec-4-ene **126**



To a solution of the β -hydroxy ketone **125** (100 mg, 0.25 mmol) in THF (15 ml) at 0 °C was added acetaldehyde (46 mg, 1.04 mmol) followed by SmI₂ (1.57 ml of a 0.1 M solution in THF) dropwise and the yellow reaction mixture stirred for 5 min. The reaction mixture was added to a mixture of potassium sodium tartrate tetrahydrate /K₂CO₃ (10:1 mixture; 30 ml; 10% aqueous) and CH₂Cl₂ (30 ml), the layers separated and the aqueous phase extracted with CH₂Cl₂ (2 x 30 ml). The combined organics were washed with NaCl (80 ml; sat.), dried (MgSO₄) and the volatiles removed under reduced pressure. Flash chromatography (10-25% EtOAc in hexane) afforded the monoester **126** as a clear, colourless oil (77 mg, 70%). R_f (20% EtOAc in hexane) = 0.44; ν_{\max} (neat)/cm⁻¹ 3456 (OH), 1717 (C=O, ester); ¹H NMR δ (200

MHz, CDCl₃) 5.44 (1H, t, $J = 7.2$ Hz, C(4)*H*), 4.79 (1H, dt=q, $J = 6.4$ Hz, C(8)*H*), 3.90-3.82 (1H, m, *CHOH*), 3.55 (2H, t, $J = 6.2$ Hz, CH₂OTBS), 2.03 (3H, s, CH₃C=O), 1.90 (2H, dd=t, $J = 7.2$ Hz, C(3)*H*₂), 1.88-1.72 (1H, m, C(2)*H*), 1.68-1.18 (11H, m, 5 x CH₂ and C(7)*H*), 1.54 (3H, s, C(5)*H*₃), 0.90-0.79 (18H, m, 3 x CH₃ and *t*-BuSi), 0.0 (6H, s, SiMe₂); ¹³C NMR δ (50.3 MHz, CDCl₃) 171.3, 135.3, 125.0, 76.0, 75.9, 63.0, 39.0, 36.6, 32.6, 30.6, 29.1, 28.6, 25.8 (3C), 25.5, 25.4, 22.3 (2C), 21.0, 18.2, 12.8, 9.3, -5.5 (2C); HRMS (FAB, MeCN/thioglycerol) [M+H]⁺ found 443.3557, C₂₅H₅₁O₄Si requires 443.3556; *m/z* 443 ([M+H]⁺ 1), 425 (10), 364 (31), 73 (100%).

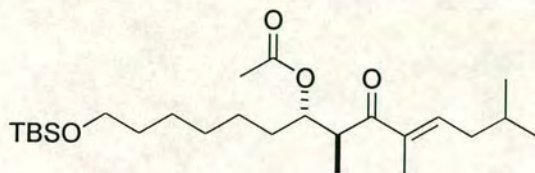
(4*E*,6*RS*,7*SR*,8*SR*)-8-Benzoyloxy-14-*t*-butyldimethylsilyloxy-6-hydroxy-2,5,7-trimethyltetradec-4-ene 127



To a solution of the β -hydroxy ketone **125** (19 mg, 0.047 mmol) in THF (10 ml) at 0 °C was added benzaldehyde (21 mg, 0.19 mmol) followed by SmI₂ (0.28 ml of a 0.1 M solution in THF) dropwise and the yellow reaction mixture stirred for 15 min. The reaction mixture was added to a mixture of potassium sodium tartrate tetrahydrate /K₂CO₃ (10:1 mixture; 15 ml; 10% aqueous) and CH₂Cl₂ (10 ml), the layers separated and the aqueous phase extracted with CH₂Cl₂ (2 x 10 ml). The combined organics were washed with NaCl (40 ml; sat.), dried (MgSO₄) and the volatiles removed under reduced pressure. Flash chromatography (5-20% EtOAc in hexane) afforded the diol monoester as a clear, colourless oil (16 mg, 70%). *R_f* (20% EtOAc in hexane) = 0.48; ν_{max} (neat)/cm⁻¹ 3458 (OH), 1721 (C=O, ester); ¹H NMR δ (200 MHz, CDCl₃) 8.03-7.02 (5H, m, Ar), 5.46 (1H, t, $J = 7.1$ Hz, C(4)*H*), 5.02 (1H, dt=q, $J = 6.8$ Hz, C(8)*H*), 3.90-3.81 (1H, d, $J = 3.8$ Hz, *CHOH*), 3.57 (2H, t, $J = 6.2$ Hz, CH₂OTBS), 1.91 (2H, dd=t, $J = 7.1$ Hz, C(3)*H*₂), 1.88-1.73 (1H, m, C(2)*H*), 1.69-1.18 (11H, m, 5 x CH₂ and C(7)*H*), 1.58 (3H, s, C(5)*H*₃), 0.92-0.78 (18H, m, 3 x CH₃

and *t*-BuSi), 0.0 (6H, s, SiMe₂). **HRMS** (FAB, MeCN/thioglycerol) [M+H]⁺ found 521.4041, C₃₁H₅₇O₄Si requires 521.4020; **m/z** 521 ([M+H]⁺ 1), 503 (14), 364 (38).

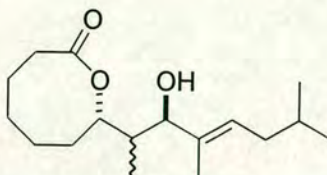
(4*E*,7*SR*,8*SR*)-8-Ethanoyloxy-14-*t*-butyldimethylsilyloxy-2,5,7-trimethyltetradec-4-en-6-one 134



General procedure B was used alcohol **126** (32 mg, 0.07 mmol) and IBX (43 mg, 0.15 mmol) in DMSO (0.5 ml) and THF (0.5 ml), and stirred at room temperature for 4 h until complete by tlc. Flash chromatography (20% EtOAc in hexane) afforded enone **134** as a clear, colourless oil (26 mg, 84%). **R_f** (20% EtOAc in hexane) = 0.44; ν_{max} (neat)/cm⁻¹ 1722 (ester), 1660 (enone); **¹H NMR** δ (200 MHz, CDCl₃) 6.81 (1H, t, *J* = 6.4 Hz, C(4)*H*), 5.01 (1H, ddd, *J* = 8.2, 7.0 & 3.2 Hz, C(8)*H*), 3.57 (1H, qd=qn, *J* = 7.0 Hz, C(7)*H*), 3.53 (2H, t, *J* = 6.7 Hz, CH₂OTBS), 2.13 (2H, dd=t, *J* = 6.4 Hz, C(3)*H*₂), 1.96 (3H, s, CH₃C=O), 1.92-1.70 (1H, m, C(2)*H*), 1.73 (3H, s, C(5)*H*₃), 1.68-1.10 (10H, m, 5 x CH₂), 1.01 (3H, d, *J* = 7.0 Hz, C(7)HCH₃), 0.88 (6H, d, *J* = 6.6 Hz, C(13)H(CH₃)₂), 0.85 (9H, s, *t*-BuSi), 0.0 (6H, s, SiMe₂); **¹³C NMR** δ (50.3 MHz, CDCl₃) 202.5, 170.4, 142.4, 137.1, 75.4, 63.0, 42.3, 38.1, 32.5, 29.5, 29.0, 28.2, 25.8 (4C), 25.4, 25.0, 22.3 (2C), 20.8, 18.1, 11.7, 11.5, -5.5.

(7*SR*,9*RS*,10*E*)-9-Hydroxy-8,10,13-trimethyltetradec-10-enoic 1,7-lactone

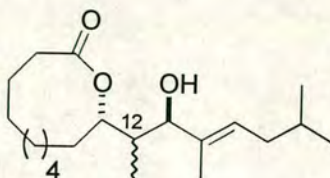
128/129



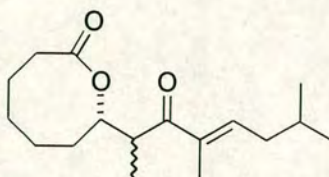
To a solution of benzaldehyde (18.5 mg, 0.174 mmol) in THF (3 ml) at 0 °C was added SmI_2 (1.74 ml of a 0.1 M solution in THF, 0.174 mmol) dropwise and the green solution was stirred for 30 min after which time the solution had become yellow (indicating formation of the Sm(III) pinacol adduct). To this solution was added a solution of aldehyde **123** (49 mg, 0.174 mmol) in THF (20 ml) slowly and dropwise over 2h and the reaction stirred for a further 2 h at room temperature. The reaction mixture was added to a mixture potassium sodium tartrate tetrahydrate/ K_2CO_3 (10:1 mixture; 30 ml; 10% aqueous) and CH_2Cl_2 (40 ml), the layers separated and the aqueous phase extracted with CH_2Cl_2 (2 x 40 ml). The combined organics were washed with NaCl (100 ml; sat.), dried (MgSO_4) and the volatiles removed under reduced pressure. Flash chromatography (20% EtOAc in hexane) afforded lactones **128** and **129** as a clear, colourless oil (15 mg, 31%). Analysis of the 600 MHz ^1H NMR showed the presence of a 1:1 mixture of diastereomers: R_f (20% EtOAc in hexane) = 0.52; ν_{max} (neat)/ cm^{-1} 3420 (OH), 1726 (C=O, lactone); ^1H NMR δ (600 MHz, CDCl_3) 5.47 (1H, tq, $J = 7.4$ & 1.3 Hz, C(11)H), 4.86-4.81 (1H, m, C(7)H), 3.88-3.85 (0.5H, m, C(9)H), 3.84-3.81 (0.5H, m, C(9)H), 2.42-2.27 (2H, m, C(2)H₂), 2.09 (0.5H, d, $J = 3.7$ Hz, OH), 2.05 (0.5H, d, $J = 3.7$ Hz, OH), 1.93 (2H, dd \equiv t, $J = 7.4$ Hz, C(12)H₂), 1.88-1.82 (1H, m, C(13)H), 1.81-1.50 (8H, m, C(8)H, C(10)CH₃ and 2 x CH₂), 1.40-1.20 (4H, m, 2 x CH₂), 0.90-0.87 (6H, m, 2 x CH₃), 0.82 (1.5H, d, $J = 7.0$ Hz, CH₃), 0.81 (1.5H, d, $J = 7.0$ Hz, CH₃); ^{13}C NMR δ (50.3 MHz, CDCl_3) 174.1, 173.8, 135.3, 135.2, 125.0, 124.8, 75.7, 75.6*, 74.7, 38.8*, 36.6*, 33.6, 33.4, 30.5*, 28.6*, 28.5, 28.2, 24.4*, 24.0*, 22.4*, 22.2*, 13.0*, 9.1, 9.0 (*=peaks common to both diastereomers); HRMS (FAB)

$[M+H]^+$ found 283.2267, $C_{17}H_{31}O_3$ requires 283.2273; m/z 283 ($[M+H]^+$ 2), 265 (20), 55 (100%).

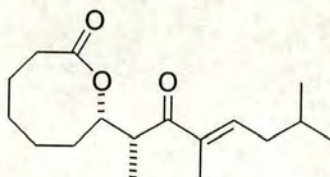
(10*SR*,12*RS*,13*E*)-12-Hydroxy-11,13,16-trimethylheptadec-13-enoic 1,10-lactone 130/131



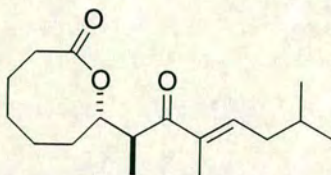
To a solution of benzaldehyde (22.0 mg, 0.174 mmol) in THF (8 ml) at 0 °C was added SmI_2 (2.31 ml of a 0.1 M solution in THF, 0.174 mmol) dropwise and the green solution was stirred for 15 min after which time the solution had become yellow (indicating formation of the Sm(III) pinacol adduct). To this solution was added a solution of aldehyde **124** (67 mg, 0.210 mmol) in THF (20 ml) slowly and dropwise and the reaction stirred for a further 20 min at 0 °C. The reaction mixture was quenched by the addition of $NaHCO_3$ (5 ml; sat.) and extracted with EtOAc (3 x 10 ml). The combined organics were washed with NaCl (20 ml; sat.), dried ($MgSO_4$) and the volatiles removed under reduced pressure. Flash chromatography (25% EtOAc in hexane) afforded lactones **130** and **131** as a clear, colourless oil (20 mg, 30%). Analysis of the 600 MHz 1H NMR showed the presence of a 1:1 mixture of diastereomers: R_f (50% EtOAc in hexane) = 0.81; ν_{max} (neat)/ cm^{-1} 3381 (OH), 1724 (C=O, lactone); 1H NMR δ (200 MHz, $CDCl_3$) 5.47 (1H, t, J = 7.3 Hz, C(14)H), 4.88-4.79 (1H, m, C(7)H), 3.92-3.82 (1H, m, C(9)H), 2.42-2.26 (2H, m, C(2)H₂), 2.13 (0.5H, d, J = 3.7 Hz, OH), 2.12 (0.5H, d, J = 3.3 Hz, OH), 1.93 (2H, dd \equiv t, J = 7.3 Hz, C(15)H₂), 1.88-1.82 (1H, m, C(13)H), 1.81-1.50 (8H, m, C(8)H, C(13)CH₃ and 2 x CH₂), 1.40-1.18 (10H, m, 5 x CH₂), 0.92-0.81 (9H, m, 3 x CH₃), ^{13}C NMR δ (50.3 MHz, $CDCl_3$) 174.4, 174.3, 135.2*, 125.0, 124.9, 75.8, 75.7, 75.5, 75.4, 39.3, 39.2, 36.6*, 35.0, 34.9, 30.8, 30.7, 29.8, 29.7, 29.6, 29.2*, 29.1, 29.0, 28.9, 28.6*, 28.5, 28.2, 25.5*, 25.4*, 22.4*, 22.3*, 13.0*, 9.3, 9.2 (*=peaks common to both diastereomers).

(7*SR*,10*E*)-9-Oxo-8,10,13-trimethyltetradec-10-enoic 1,7-lactone 132/133

General procedure B was used with alcohol **128/129** (20.0 mg, 0.071 mmol) and IBX (38.0 mg, 0.142 mmol) in DMSO (0.5 ml) and THF (0.5 ml), and stirred at room temperature for 20 h until complete by tlc. Careful flash chromatography (5-25% EtOAc in hexane) allowed the separation of 2 diastereomers **132** (9.0 mg, 45%) and **133** (8.9 mg, 45%).

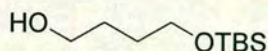
(7*SR*,8*RS*,10*E*)-9-Oxo-8,10,13-trimethyltetradec-10-enoic 1,7-lactone 133

Tentative assignment: enone 133: R_f (20% EtOAc in hexane) = 0.47; ν_{\max} (neat)/ cm^{-1} 1726 (C=O, lactone), 1658 (C=O, enone); $^1\text{H NMR}$ δ (200 MHz, CDCl_3) 6.89 (1H, t, $J = 7.3$ Hz, C(11)*H*), 5.06-5.00 (1H, m, C(7)*H*), 3.67 (1H, dq \equiv qn, $J = 6.6$ Hz, C(8)*H*), 2.32-2.22 (2H, m, C(2)*H*₂), 2.18 (2H, dd \equiv t, $J = 7.0$ Hz, C(12)*H*₂), 1.90-1.75 (1H, m, C(13)*H*), 1.75 (3H, s, C(10)*CH*₃), 1.65-1.20 (8H, m, 4 x *CH*₂), 1.00 (3H, d, $J = 6.6$ Hz, C(8)*HCH*₃), 0.98 (3H, d, $J = 6.6$ Hz, C(13)*H(CH*₃)_A(*CH*₃)_B), 0.96 (3H, d, $J = 6.6$ Hz, C(13)*H(CH*₃)_A(*CH*₃)_B); $^{13}\text{C NMR}$ δ (50.3 MHz, CDCl_3) 202.5, 172.8, 142.8, 137.1, 74.5, 41.6, 38.2, 33.8, 28.8, 28.3 (2C), 24.6, 23.8, 22.4 (2C), 11.6, 11.2; **HRMS** (EI) $[\text{M}+\text{H}]^+$ not found, 2 fragments found 125.0961 and 183.1020, $\text{C}_8\text{H}_{13}\text{O}$ and $\text{C}_{10}\text{H}_{15}\text{O}_3$ require 125.0966 and 183.1021 respectively; m/z (FAB) 281 ($[\text{M}+\text{H}]^+$ 7), 263 (4), 125 (44), 92 (100%).

(7*SR*,8*SR*,10*E*)-9-Oxo-8,10,13-trimethyltetradec-10-enoic 1,7-lactone 132

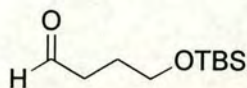
Tentative assignment: enone **132**: R_f (20% EtOAc in hexane) = 0.44; ν_{\max} (neat)/ cm^{-1} 1731, 1665 cm^{-1} ; $^1\text{H NMR}$ δ (250 MHz, CDCl_3) 6.78 (1H, td, $J = 7.3$ & 1.2 Hz, C(11)*H*), 5.07-5.01 (1H, m, C(7)*H*), 3.58 (1H, dq=qn, $J = 7.0$ Hz, C(8)*H*), 2.23 (2H, t, $J = 6.0$ Hz, C(2)*H*₂), 2.15 (2H, dd, $J = 7.3$ & 6.6 Hz, C(12)*H*₂), 1.84 (1H, m, C(13)*H*), 1.72 (3H, d, $J = 1.2$ Hz, C(10)*CH*₃), 1.71-1.20 (8H, m, 4 x *CH*₂), 1.02 (3H, d, $J = 7.0$ Hz, C(8)*HCH*₃), 0.96 (3H, d, $J = 6.6$ Hz, C(13)*H(CH*₃)_A(*CH*₃)_B)), 0.94 (3H, d, $J = 6.6$ Hz, C(13)*H(CH*₃)_A(*CH*₃)_B)); $^{13}\text{C NMR}$ δ (62.9 MHz, CDCl_3) 202.7, 172.9, 142.3, 137.2, 75.4, 42.0, 38.2, 33.6, 29.6, 28.6, 28.3, 24.4, 24.2, 22.4 (2C), 12.5, 11.7; **HRMS** (Electrospray) $[\text{M}+\text{H}]^+$ found 283.2129, $\text{C}_{17}\text{H}_{29}\text{O}_3$ requires 283.2117 m/z (FAB) 281 ($[\text{M}+\text{H}]^+ 4$), 263 (3), 92 (82), 74 (100%).

5.3 EXPERIMENTAL FOR CHAPTER 3

4-*t*-Butyldimethylsilyloxybutan-1-ol **141**

General procedure A was used with butane-1,4-diol (1.50 ml, 16.92 mmol), sodium hydride (677 mg, 16.92 mmol) and TBSCl (2.55 g, 16.92 mmol) in THF (15 ml). Flash chromatography (30% EtOAc in hexane) afforded the monosilylated diol **141** as a clear, colourless oil (3.07 g, 89%). R_f (20% EtOAc in hexane) 0.32; ν_{\max} (neat)/ cm^{-1} 3357 (OH); $^1\text{H NMR}$ δ (200 MHz, CDCl_3) 3.67-3.50 (4H, m, CH_2OH and CH_2OTBS), 2.50 (1H, br s, OH), 1.70-1.39 (6H, m, 3 x CH_2), 0.83 (9H, s, *t*-BuSi), 0.00 (6H, s, SiMe_2).

$^1\text{H NMR}$ spectroscopic data in agreement with the literature.⁷⁴

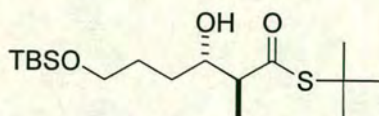
4-*t*-Butyldimethylsilyloxybutanal **140**

General procedure B was used for monoprotected alcohol **141** (2.00 g, 9.80 mmol) and IBX (5.49 g, 19.60 mmol) in DMSO (25 ml) and THF (30 ml) and stirred for 2 h at room temperature. Flash chromatography (15% EtOAc in hexane) gave aldehyde **140** as a clear, colourless oil (1.69 g, 85%). R_f (20% EtOAc in hexane) = 0.59; ν_{\max} (neat)/ cm^{-1} 2715 (C-H, aldehyde) 1728 (C=O); $^1\text{H NMR}$ δ (200 MHz, CDCl_3) 9.75 (1H, t, J = 1.8 Hz, HC(O)), 3.61 (2H, t, J = 5.9 Hz, CH_2OTBS), 2.43 (2H, td, J = 7.2 Hz and 1.8 Hz, $\text{CH}_2\text{C(O)}$), 1.88-1.75 (2H, m, C(3)H_2), 0.84 (9H, s, *t*-BuSi), 0.00 (6H, s, SiMe_2).

$^1\text{H NMR}$ spectroscopic data in agreement with the literature.¹⁴⁰

***t*-Butyl (2*SR*,3*SR*)-6-*t*-butyldimethylsilyloxy-3-hydroxy-2-methyl hexanthioate**

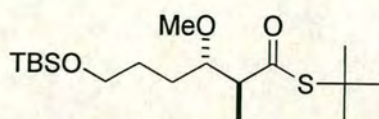
139



General procedure C was used with thioester **88** (460 mg, 3.15 mmol), dicyclohexylbromoborane (874 mg, 3.57 mmol) and triethylamine (526 μ l, 3.78 mmol) added. Aldehyde **140** (425 mg, 2.10 mmol) was added and the reaction mixture stirred for 1 h at -78°C . Flash chromatography (gradient elution, 5-15% EtOAc in hexane) gave the aldol adduct **139** as a clear, colourless oil (593 mg, 81%). Analysis of the 200 MHz ^1H NMR showed the presence of a single diastereomer, the *anti* aldol product. R_f (20% EtOAc in hexane) = 0.60 ; ν_{max} (neat)/ cm^{-1} 3421 (OH), 1680 (C=O); ^1H NMR δ (200 MHz, CDCl_3) 3.62-3.52 (3H, m, CHOH and CH_2OTBS), 2.95 (1H, d, $J = 6.9$ Hz, OH), 2.59 (1H, qd \equiv qn, $J = J' = 7.0$, C(2)H), 1.65-1.42 (4H, m, 2 x CH_2), 1.40 (9H, s, *t*-BuS), 1.13 (3H, d, $J = 7.0$ Hz, C(2) CH_3), 0.83 (9H, s, *t*-BuSi), 0.00 (6H, s, SiMe₂); ^{13}C NMR δ (50.3 MHz, CDCl_3) 204.8, 73.5, 63.0, 53.6, 48.0, 31.6, 29.6 (3C), 28.8, 25.8 (3C), 18.1, 14.7, -5.5 (2C); HRMS (FAB, MeCN/thioglycerol) $[\text{M}+\text{H}]^+$ found 349.2238, $\text{C}_{17}\text{H}_{37}\text{O}_3\text{SSi}$ requires 349.2233; m/z 349 ($[\text{M}+\text{H}]^+$ 26), 259 (48), 241 (13%).

***t*-Butyl (2*SR*,3*SR*)-6-*t*-butyldimethylsilyloxy-3-methoxy-2-methylhexanthioate**

138

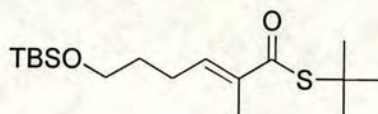


To a solution of **139** (186 mg, 0.53 mmol) in CH_2Cl_2 (10 ml) was added Proton sponge[®] (458mg, 2.14 mmol) and trimethyloxonium tetrafluoroborate (300 mg, 2.03 mmol) and the reaction stirred at room temperature for 2 h. H_2O (15 ml) was added

and the solution extracted with EtOAc (3 x 15 ml), dried (MgSO₄) and the solvents removed under reduced pressure to afford an oil which was purified by passing through a small pad of silica and eluting with CH₂Cl₂. This gave **138** as a colourless oil 180 mg (94%). R_f (20% EtOAc in hexane) = 0.87; ν_{\max} (neat)/cm⁻¹ 3421 (OH), 1682 (C=O); ¹H NMR δ (200 MHz, CDCl₃) 3.57 (2H, t, J = 6.0 Hz, CH₂OTBS), 3.42 (1H, ddd, J = 8.0, 7.3 & 1.8 Hz, CHOMe), 3.29 (3H, s, OCH₃), 2.72 (1H, qd=qn, J = J' = 7.3, C(2)H), 1.65-1.41 (4H, m, 2 x CH₂), 1.42 (9H, s, *t*-BuS), 1.01 (3H, d, J = 7.3 Hz, C(2)CH₃), 0.84 (9H, s, *t*-BuSi), 0.00 (6H, s, SiMe₂); ¹³C NMR δ (62.9 MHz, CDCl₃) 202.9 (C), 82.3 (CH), 63.0 (CH₂), 57.8 (CH₃), 51.8 (CH), 47.6 (C), 29.6 (3CH₃), 27.8 (CH₂), 26.5 (CH₂), 25.8 (3CH₃), 18.2 (C), 12.7 (CH₃), -5.4 (2CH₃); HRMS (FAB, MeCN/thioglycerol) [M+H]⁺ found 363.2382, C₁₈H₃₉O₃SSi requires 363.2389; m/z 363 ([M+H]⁺ 19), 305 (44), 273 (65%).

Attempted *O*-Methylation of aldol adduct **139**

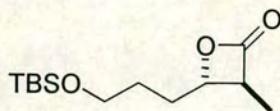
Synthesis of *t*-Butyl-6-*t*-butyldimethylsilyloxy-2-methylhex-2-enethioate **142**



To a stirred solution of alcohol **139** (56 mg, 0.161 mmol) in THF (5 ml) was added NaHMDS (0.6 M solution in toluene, 359 μ l, 0.209 mmol) at -78 °C dropwise. The solution was stirred at that temperature for 5 min before adding methyl iodide (50 μ l, 0.804 mmol) dropwise and stirred for a further 20 min. The reaction mixture was quenched by the addition of NH₄Cl (20 ml, sat.) and the mixture extracted with CH₂Cl₂ (3 x 20 ml). The organics were washed with NaCl (40 ml, sat.), dried (MgSO₄) and the volatiles removed under reduced pressure. Flash chromatography (20% EtOAc in hexane) afforded **142** as a clear, colourless oil (22 mg, 42%). R_f (20% EtOAc in hexane) = 0.90; ¹H NMR δ (200 MHz, CDCl₃) 6.63 (1H, t, J = 7.3 Hz, CH olefin), 3.59 (2H, t, J = 6.2 Hz, CH₂OTBS), 2.21 (2H, dt, J = J' = 7.3 Hz, CH₂CH=C), 1.79 (3H, s, CH₃C=CH), 1.72-1.55 (2H, m, C(5)H₂), 1.45 (9H, s, *t*-BuS), 1.01 (3H, d, J = 7.3 Hz, C(2)CH₃), 0.86 (9H, s, *t*-BuSi), 0.00 (6H, s, SiMe₂).

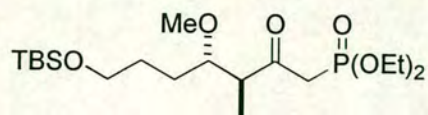
Attempted *O*-Methylation of aldol adduct **139**

Synthesis of (2*SR*,3*SR*)-6-*t*-butyldimethylsilyloxy -2-methylhexanoic 1,3-lactone **143**



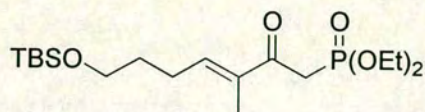
To a stirred solution of alcohol **139** (44 mg, 0.126 mmol) in THF (2 ml) was added potassium HMDS (0.5 M solution in toluene, 278 μ l, 0.139 mmol) at $-78\text{ }^{\circ}\text{C}$ dropwise. The solution was stirred at that temperature for 5 min before adding methyl iodide (78 μ l, 1.26 mmol) dropwise and stirred for a further 20 min. The reaction mixture was quenched by the addition of NH_4Cl (20 ml, sat.) and the mixture extracted with CH_2Cl_2 (3 x 20 ml). The organics were washed with NaCl (40 ml, sat.), dried (MgSO_4) and the volatiles removed under reduced pressure. Flash chromatography (3% EtOAc in CH_2Cl_2) afforded **143** as a clear, colourless oil (13 mg, 40%). R_f (20% EtOAc in hexane) = 0.70 ; ν_{max} (neat)/ cm^{-1} 1826 cm^{-1} ($\text{C}=\text{O}$); ^1H NMR δ (200 MHz, CDCl_3) 4.18 (1H, ddd, $J = 7.0, 6.6 \text{ \& } 4.0$ Hz, C(3)*H*), 3.61 (2H, t, $J = 6.1$ Hz, CH_2OTBS), 3.18 (1H, qd, $J = 7.5 \text{ \& } 4.0$ Hz, C(2)*H*), 1.88-1.74 (2H, m, C(4)*H*₂), 1.68-1.48 (2H, m, C(5)*H*₂), 1.34 (3H, d, $J = 7.5$ Hz, C(2)*CH*₃), 0.87 (9H, s, *t*-BuSi), 0.02 (6H, s, SiMe₂).

(3*SR*,4*SR*)-7-*t*-Butyldimethylsilyloxy-4-methoxy-1-diethoxyphosphoryl-3-methyl-heptan-2-one (±)-3



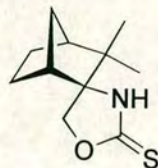
General procedure A was followed with diethylethanephosphonate (127 mg, 0.833 mmol) in THF (3 ml) to which was added ⁿBuLi (571 μl of a 1.46M solution, 0.833 mmol) and cannulated into the solution of thioester **138** (127 mg, 0.139 mmol) in THF (3 ml). Flash chromatography (EtOAc) and HPLC (50% EtOAc in Hexane) afforded the β-ketophosphonate (±)-**3** (38 mg, 64%) and the unsaturated product **144** (6 mg, 9%) as clear oils. **Major product**: *R_f* (50% EtOAc in hexane) = 0.20; *ν*_{max} (neat)/cm⁻¹ 1715 (C=O), 1253 (P=O), 1026 (P-O); ¹H NMR δ (250 MHz, CDCl₃) 4.20-4.06 (4H, m, P(OCH₂CH₃)₂), 3.57 (2H, t, *J* = 6.0 Hz, CH₂OTBS), 3.40-3.33 (1H, m, C(4)*H*), 3.32 (1H, dd, *J* = 22.7 & 14.0 Hz, CH_AH_BP(O)), 3.24 (3H, s, OCH₃), 3.11-2.97 (1H, m, C(3)*H*), 3.05 (1H, dd, *J* = 22.7 & 14.0 Hz, CH_AH_BP(O)), 1.70-1.40 (4H, m, C(5)*H*₂ and C(6)*H*₂), 1.32 (6H, t, *J* = 7.1 Hz, P(OCH₂CH₃)₂), 1.00 (3H, d, *J* = 6.9 Hz, C(3)CH₃), 0.88 (9H, s, *t*-BuSi), 0.03 (6H, s, SiMe₂); ¹³C NMR δ (62.9 MHz, CDCl₃) 205.9 (d, ²*J*_{P-C} = 6.1 Hz), 83.1, 62.9, 62.3 (2C, d, ²*J*_{P-C} = 3.5 Hz), 57.3, 49.5, 43.2 (d, ¹*J*_{P-C} = 128 Hz), 27.0, 26.1, 25.8, (3C), 18.2, 16.3, 16.2, 12.3, -5.45; ³¹P NMR δ (101.3 MHz) 21.2 (*P*=O); *m/z* (FAB, thioglycerol) 425 ([*M*+*H*]⁺ 48%), 393 (78), 209 (19), 179 (32), 73 (100).

¹H NMR spectroscopic data in good agreement with the literature.¹⁴¹

7-*t*-Butyldimethylsilyloxydiethoxyphosphoryl-3-methyl-hept-3-en-2-one 144**Minor product:**

R_f (50% EtOAc in hexane) = 0.23; ν_{\max} (neat)/ cm^{-1} 1640 (C=O), 1250 (P=O), 1021 (P-O); $^1\text{H NMR}$ δ (200 MHz, CDCl_3) 6.60 (1H, t, $J = 7.7$ Hz, CH olefin), 4.20-4.06 (4H, m, $\text{P}(\text{OCH}_2\text{CH}_3)_2$), 3.60 (2H, t, $J = 6.2$ Hz, CH_2OTBS), 3.32 (2H, d, $J = 22.6$ Hz, $\text{CH}_2\text{P}(\text{O})$), 3.21 (3H, s, OCH_3), 2.26 (2H, dt, $J = J' = 7.7$ Hz, $\text{CH}_2\text{CH}=\text{C}$), 1.76 (3H, s, $\text{CH}_3\text{C}=\text{CH}$), 1.64-1.40 (2H, m, $\text{C}(6)\text{H}_2$), 1.29 (6H, t, $J = 7.0$ Hz, $\text{P}(\text{OCH}_2\text{CH}_3)_2$), 0.97 (3H, d, $J = 7.0$ Hz, $\text{C}(3)\text{CH}_3$), 0.84 (9H, s, *t*-BuSi), 0.00 (6H, s, SiMe_2).

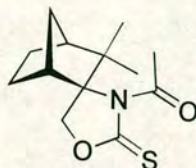
5.4 EXPERIMENTAL FOR CHAPTER 4

(5*S*, 7*S*, 10*R*)-2-oxa-4-aza-6,6-dimethyl-7,10-methylenespiro[4.5]decan-3-thione
147

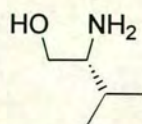
To a solution of amino alcohol **146** (102 mg, 0.60 mmol) in THF (8 ml) at room temperature was added Et₃N (402 μ l, 2.86 mmol) followed by CS₂ (215 μ l, 3.57 mmol). The resulting mixture was then heated under reflux for 16h. The volatiles were removed under reduced pressure, the brown residue dissolved in CH₂Cl₂ (5 ml), washed with H₂O (5 ml), NaCl (5 ml; sat.), dried (MgSO₄) and the solvent removed under reduced pressure. Flash chromatography (5% MeOH in CH₂Cl₂) afforded a clear oil which was triturated with hexane to give an off-white crystalline solid **147** (104 mg, 84%).[†] *R_f* (CH₂Cl₂) 0.21; *MP* 207-209 °C; ¹H NMR δ (200 MHz, CDCl₃) 8.89 (1H, br s, N-H), 4.56 (1H, d, *J* = 9.5 Hz, C(1)*H_A*CH_B), 4.45 (1H d, *J* = 9.5 Hz, C(1)*H_A*CH_B), 2.29-2.20 (1H, m, C(10)*H*), 1.89-1.72 (2H, m), 1.64-1.43 (2H, m), 1.41-1.06 (3H, m), 1.01 (3H, s, CH₃), 0.98 (3H, s, CH₃); ¹³C NMR δ (50.3 MHz, CDCl₃) 187.6, 74.1, 48.5, 47.9, 42.9, 35.2, 26.2, 24.0, 23.4, 21.9 (2C); **HRMS** (FAB, MeCN/thioglycerol) [M+H]⁺ found 213.1090, C₁₁H₁₇NOS requires 213.1109; *m/z* (FAB) 211 ([M]⁺ 100%); **Crystal Structure** For crystal structure and associated data see **Appendix**.

[†] A small sample was recrystallised from CH₂Cl₂/hexane to give several good crystals of the title compound.

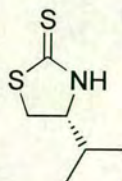
N*-Acetyl-(5*S*, 7*S*, 10*R*)-2-oxa-4-aza-6,6-dimethyl-7,10-methylenespiro-[4.5]-decan-3-thione **145*



To a suspension of NaH (60% suspension in mineral oil prewashed with dry hexane) (24 mg, 0.590 mmol) in THF (5 ml) was added a solution of thiazolidinethione **147** (82 mg, 0.390 mmol) in THF (5 ml + 5 ml washings) at 0 °C and stirred at that temperature for 25 min. Freshly distilled acetyl chloride (34 μ l, 0.470 mmol) was added dropwise and the reaction stirred at 0 °C for a further 30 min. The turbid solution was very carefully quenched with H₂O (2 ml) and the THF removed under reduced pressure. The residue was extracted with CH₂Cl₂ (10 ml), washed with NaHCO₃ (2 x 10 ml; sat.), NaCl (10 ml; sat.), dried (MgSO₄) and the volatiles removed under reduced pressure. Flash chromatography (CH₂Cl₂) afforded the acetate **145** as a colourless crystalline solid (75 mg, 76%). R_f (CH₂Cl₂) = 0.67; ¹H NMR δ (200 MHz, CDCl₃) 4.48 (1H, d, J = 9.4 Hz, C(1)*H_A*CH_B), 4.45 (1H d, J = 9.4 Hz, C(1)*H_A*CH_B), 2.76-2.68 (1H, m), 2.73 (3H, s, CH₃C(O)), 2.64-2.59 (1H, m), 1.89-1.82 (1H, m), 1.68-1.43 (4H, m), 1.26 (1H, dt, J = 10.6 & 1.1 Hz), 1.21-1.03 (1H, m), 1.16 (3H, s, CH₃), 1.05 (3H, s, CH₃); ¹³C NMR δ (50.3 MHz, CDCl₃) 189.9, 80.7, 74.6, 49.4, 48.0, 44.8, 38.1, 27.9, 25.5, 25.2, 22.5, 21.6 (2C); HRMS (FAB, MeCN/thioglycerol) [M+H]⁺ found 254.1204, C₁₃H₂₀NO₂S requires 254.1215; m/z (FAB) 254 ([M]⁺ 100), 212 (88%).

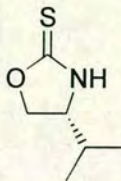
(R)-Valinol [(R)-2-Amino-3-methyl-1-butanol] 150

To a stirred mixture of NaBH_4 (8.67 g, 229 mmol) in THF (200 ml) at 0 °C was added *R*-valine (9.98 g, 84.9 mmol) in one portion. Iodine (21.56 g, 84.9 mmol) in THF (75 ml + 75 ml washings) was added slowly *via* a dropping funnel. When the yellow hue had subsided (*c.* 20 minutes) the reaction was heated under reflux for 20 h. The mixture was cooled to room temperature and MeOH (80 ml) added carefully and dropwise until a clear solution was obtained. The volatiles were then removed under reduced pressure to afford a thick paste which was dissolved in KOH (800 ml; 20% aqueous) and stirred for a further 15 h. The solution was extracted with CH_2Cl_2 (4 x 200 ml), dried (MgSO_4) and the volatiles removed under reduced pressure. Distillation of the crude product afforded valinol **150** as a colourless, crystalline, low melting point solid (5.39 g, 62%). **MP** 34-35 °C, *lit.*¹⁴² 35-36 °C; **BP** 84 °C (9 mm Hg), *lit.*¹⁴² 81 °C (8 mm Hg); $[\alpha]_{\text{D}}^{23} = -14.0^\circ$ (*c* 1.1, EtOH), *lit.*¹⁴² -14.3° (*c* 1.11, EtOH); $^1\text{H NMR}$ δ (200 MHz, CDCl_3) 3.62 (1H, dd, $J = 10.3$ & 3.3 Hz, $\text{C}(1)\text{H}_\text{X}\text{H}_\text{Y}$), 3.26 (1H, dd, $J = 10.3$ & 8.7 Hz, $\text{C}(1)\text{H}_\text{X}\text{H}_\text{Y}$), 2.65-2.48 (1H, m, $\text{C}(2)\text{H}$), 2.11-1.70 (3H, m, NH_2 and OH), 1.55 (1H, dspt≡oct, $J = 6.8$ Hz, $\text{C}(3)\text{H}$), 0.91 (3H, d, $J = 6.8$ Hz, $\text{C}(3)\text{H}(\text{CH}_3)_\text{A}(\text{CH}_3)_\text{B}$), 0.88 (3H, d, $J = 6.8$ Hz, $\text{C}(3)\text{H}(\text{CH}_3)_\text{A}(\text{CH}_3)_\text{B}$).

(4*R*)-4-(Isopropyl)-2-thiazolidinethione 151

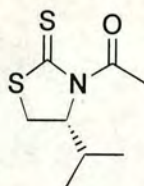
To a solution of *R*-valinol **150** (4.75 g, 46.1 mmol) in KOH (58.3 ml, 230 mmol; 1*N* aqueous), was added carbon disulfide (13.86 ml, 230 mmol) and the mixture heated under reflux for 22 h. The reaction was cooled to room temperature, extracted with CH₂Cl₂ (3 x 50 ml), dried (MgSO₄) and the volatiles removed under reduced pressure. Flash chromatography (30% EtOAc in hexane) to remove some unreacted oxazolidinethione **152** (1.10 g, 16%) (this could be converted to the desired thiazolidinethione by further treatment with carbon disulfide and KOH) afforded **151** as a colourless, crystalline solid (4.80 g, 65%). *R_f* (50% EtOAc in hexane) = 0.80; *MP* 68–69 °C, lit.¹¹¹; $[\alpha]_D^{23} = +19.2^\circ$ (*c* 8.0, CHCl₃), lit.¹¹¹ +19.2° (*c* 8.0, CHCl₃); ¹H NMR δ (200 MHz, CDCl₃) 8.10 (1H, brs, NH), 4.05 (1H, ddd, *J* = 8.2, 8.2 & 6.6 Hz, C(4)*H*), 3.50 (1H, dd, *J* = 11.1 & 8.2 Hz, C(5)*H_XH_Y*), 3.31 (1H, dd, *J* = 11.1 & 8.2 Hz, C(5)*H_XH_Y*), 1.55 (1H, dspt≡oct, *J* = 6.6 Hz, C(3)*H*), 0.91 (3H, d, *J* = 6.7 Hz, C(4)CH(CH₃)_A(CH₃)_B), 0.88 (3H, d, *J* = 6.7 Hz, C(4)CH(CH₃)_A(CH₃)_B); ¹³C NMR δ (50.3 MHz, CDCl₃) 200.7, 69.9, 35.5, 31.8, 18.6, 18.0; HRMS (CI, NH₃) [*M*]⁺ found 161.0333, C₆H₁₁NS₂ requires 161.0333; *m/z* 162 ([*M*+*H*]⁺ 100), 130 (23%).

¹H NMR and ¹³C NMR spectroscopic data in good agreement with that of the literature.¹¹¹

(4*R*)-4-(Isopropyl)-2-oxazolidinethione 152

R_f (50% EtOAc in hexane) = 0.80; **MP** 44-45 °C, lit.¹¹¹ 45-46 °C; $[\alpha]_D^{23} = +21.9^\circ$ (c 0.40, CHCl₃), $^1\text{H NMR}$ δ (200 MHz, CDCl₃) 8.75 (1H, brs, NH), 4.66 (1H, t, $J = 9.1$ Hz, C(5) H_XH_Y), 4.35 (1H, dd, $J = 9.1$ & 6.8 Hz, C(5) H_XH_Y), 4.05 (1H, dt, $J = 9.1$ & 6.8 Hz, C(4) H), 1.55 (1H, m, C(3) H), 0.91 (3H, d, $J = 7.0$ Hz, C(4)CH(CH₃)_A(CH₃)_B), 0.88 (3H, d, $J = 6.6$ Hz, C(4)CH(CH₃)_A(CH₃)_B).

$^1\text{H NMR}$ spectroscopic data in good agreement with that of the literature.¹¹¹

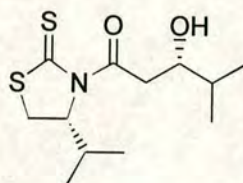
(4*R*)-*N*-Ethanoyl-4-isopropyl-2-thiazolidinethione 149

To a suspension of NaH (902 mg, 22.55 mmol, 60% suspension in mineral oil washed with dry hexane) in THF (40 ml) was added a solution of *R*-thiazolidinethione **151** (1.68 g, 10.43 mmol) in THF (6 ml + 6 ml washings) at 0 °C and stirred at that temperature for 20 min. Acetyl chloride (1.44 ml, 20.30 mmol) was added dropwise and the reaction stirred at 0 °C for a further 1 h. The turbid solution was very carefully quenched with H₂O (5 ml), neutralised with HCl (1*N* aqueous) and extracted with EtOAc (3 x 100 ml). The organic extracts were washed with NaCl (250 ml; sat.), dried (MgSO₄) and the volatiles removed under reduced pressure. Flash chromatography (30% EtOAc in hexane) afforded the acetate **149** as a bright yellow oil (2.07 g, 98%). R_f (20% EtOAc in hexane) = 0.62; **Chiral HPLC** (Chiracel OD column) **Rt** (5% *i*-PrOH in hexane) 17.5 min; $[\alpha]_D^{23} = -453.1^\circ$ (c 0.48, CHCl₃);

ν_{\max} (neat)/ cm^{-1} 1694 (C=O); ^1H NMR δ (200 MHz, CDCl_3) 5.13 (1H, ddd=dt, J = 8.0 & 6.2 Hz, C(4) H), 3.48 (1H, dd, J = 11.3 & 8.3 Hz, C(5) H_XH_Y), 2.99 (1H, d, J = 11.3, C(5) H_XH_Y), 2.75 (3H, s, $\text{CH}_3\text{C}(\text{O})$), 2.42-2.26 (1H, m, C(4) CH), 1.03 (3H, d, J = 7.0 Hz, C(4) $\text{CH}(\text{CH}_3)_A(\text{CH}_3)_B$), 0.94 (3H, d, J = 7.0 Hz, C(4) $\text{CH}(\text{CH}_3)_A(\text{CH}_3)_B$); ^{13}C NMR δ (50.3 MHz, CDCl_3) 203.1, 170.6, 71.1, 30.5, 30.2, 26.7, 18.8, 17.5; HRMS (CI, NH_3) $[\text{M}+\text{H}]^+$ found 204.0517, $\text{C}_8\text{H}_{14}\text{NOS}_2$ requires 204.0517; m/z 204 ($[\text{M}+\text{H}]^+$ 100), 174 (18), 162 (26), 130 (60%).

^1H NMR and ^{13}C NMR spectroscopic data in good agreement with that of the literature.⁷³

(3'*S*,4*R*)-3-(3'-Hydroxy-4'-methyl-1'-oxo-pentanyl)-4-isopropyl-2-thiazolidine thione 156

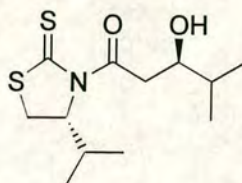


To a solution of *R*-acetyl thiazolidinethione **149** (800 mg, 4.20 mmol) in CH_2Cl_2 (15 ml) at -78°C was added TiCl_4 (0.78 ml, 7.12 mmol), followed after 15 min by DIPEA (1.31 ml, 7.54 mmol) dropwise. The deep red solution was stirred at -78°C for 25 min. Isobutyraldehyde (0.76 ml, 8.40 mmol) was added dropwise and the solution stirred for a further 20 min. The reaction was quenched by the addition of NH_4Cl (25 ml; sat.) and the reaction warmed to room temperature. The aqueous phase was extracted with CH_2Cl_2 (2 x 20 ml), the organics combined, dried (MgSO_4) and the volatiles removed under reduced pressure. Flash chromatography (5% EtOAc in CH_2Cl_2) afforded aldol adduct **156** as a clear, yellow oil (809 mg, 70%) and the minor diastereomer **157** as a clear, yellow oil (15 mg, 2%). **Major diastereomer:** R_f (10% EtOAc in CH_2Cl_2) = 0.51; $[\alpha]_D^{23} = -367^\circ$ (c 1.25, CHCl_3); ν_{\max} (neat)/ cm^{-1} 3482 (OH), 1688 (C=O); ^1H NMR δ (250 MHz, CDCl_3) 5.15 (1H, ddd, J = 8.0, 6.2 & 1.0 Hz, C(4) H), 3.91 (1H, dddd, J = 10.0, 5.9, 3.9 & 2.1 Hz, C(3') H), 3.55 (1H, dd, J = 17.7 & 2.1 Hz, C(2') H_AH_B), 3.51 (1H, dd, J = 11.4 & 8.0 Hz, C(5) H_XH_Y),

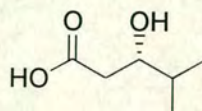
3.14 (1H, dd, $J = 17.7$ & 10.0 Hz, C(2')H_AH_B), 3.02 (1H, dd, $J = 11.4$ & 1.0 Hz, C(5)H_XH_Y), 2.71 (1H, d, $J = 3.9$ Hz, OH), 2.40-2.32 (1H, m, C(4)CH), 1.78-1.70 (1H, m, C(4')H), 1.06 (3H, d, $J = 6.7$ Hz, C(4)CH(CH₃)_A(CH₃)_B), 0.97 (3H, d, $J = 6.7$ Hz, C(4)CH(CH₃)_A(CH₃)_B), 0.96 (3H, d, $J = 5.2$ Hz, C(4')H(CH₃)_A(CH₃)_B), 0.93 (3H, d, $J = 5.2$ Hz, C(4')H(CH₃)_A(CH₃)_B); ¹³C NMR δ (50.3 MHz, CDCl₃) 203.0, 173.6, 72.5, 71.3, 42.7, 33.0, 30.7, 30.5, 19.0, 18.4, 17.8, 17.7; HRMS (FAB, thioglycerol) [M+H]⁺ found 276.1098, C₁₂H₂₂NO₂S₂ requires 276.1092; m/z 276 ([M+H]⁺ 46), 258 (27), 162 (100), 97 (41), 91 (43), 73 (96%).

Minor diastereomer

(3'*R*,4*R*)-3-(3'-Hydroxy-4'-methyl-1'-oxo-pentanyl)-4-(isopropyl)-2-thiazolidine thione 157

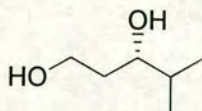


R_f (10% EtOAc in CH₂Cl₂) = 0.53; $[\alpha]_D^{23} = -204.1^\circ$ (c 1.30, CHCl₃); ν_{\max} (neat)/ cm⁻¹ 3448 (OH), 1688 (C=O); ¹H NMR δ (250 MHz, CDCl₃) 5.18 (1H, ddd, $J = 7.7$, 6.6 & 1.1 Hz, C(4)H), 3.86-3.75 (1H, m, C(3')H), 3.51 (1H, dd, $J = 11.7$ & 7.7 Hz, C(5)H_XH_Y), 3.48 (1H, dd, $J = 17.2$ & 10.0 Hz, C(2')H_AH_B), 3.28 (1H, dd, $J = 17.2$ & 2.6 Hz, C(2')H_AH_B), 3.02 (1H, dd, $J = 11.7$ & 1.1 Hz, C(5)H_XH_Y), 2.71 (1H, d, $J = 3.9$ Hz, OH), 2.40-2.32 (1H, m, C(4)CH), 1.78-1.70 (1H, m, C(4')H) 1.06 (3H, d, $J = 6.7$ Hz, C(4)CH(CH₃)_A(CH₃)_B), 0.97 (3H, d, $J = 6.7$ Hz, C(4)CH(CH₃)_A(CH₃)_B), 0.96 (3H, d, $J = 5.2$ Hz, C(4')H(CH₃)_A(CH₃)_B), 0.93 (3H, d, $J = 5.2$ Hz, C(4')H(CH₃)_A(CH₃)_B); ¹³C NMR δ (50.3 MHz, CDCl₃) 203.3, 174.1, 73.1, 71.3, 42.1, 33.2, 30.6, 30.4, 18.9, 18.3, 17.7 (2C); HRMS (FAB, thioglycerol) [M+H]⁺ found 276.1091, C₁₂H₂₂NO₂S₂ requires 276.1092; m/z 276 ([M+H]⁺ 42), 258 (22), 162 (100), 97 (42), 91 (37), 73 (91%).

(3*S*)-3-Hydroxy-4-methylpentanoic acid 158

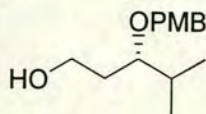
To a solution of aldol adduct **156** (60 mg, 0.22 mmol) in THF/H₂O (3:1, 1.5 ml) was added LiOH.H₂O (37 mg, 0.88 mmol) in H₂O₂ (135 µl; 30% aqueous) dropwise at 0 °C and the reaction stirred at 0 °C for 1 h. Sodium sulfite (2 ml; sat.) was added and the THF removed under reduced pressure. The mixture was diluted with H₂O (5 ml) and extracted with CH₂Cl₂ (3 x 10 ml), the organics dried (MgSO₄) and the volatiles removed under reduced pressure to afford the recovered auxiliary as a white crystalline solid **151** (31 mg, 87%). The aqueous phase was acidified with 4M HCl and extracted with diethyl ether (3 x 10 ml). The solution was dried (MgSO₄) and the volatiles removed under reduced pressure to afford **158** as a colourless oil (29 mg, 99%). $[\alpha]_D^{23} = -34.1^\circ$ (*c* 0.95, CHCl₃), lit.³⁵ -40.7° (*c* 3.0, CHCl₃); ¹H NMR δ (250 MHz, CDCl₃) 6.41 (2H, br s, COOH and OH), 3.79 (1H, ddd, C(3)HOH, *J* = 9.0, 5.8, & 3.5 Hz), 2.53 (1H, dd, *J* = 16.3 & 3.5 Hz, C(2)*H_AH_B*), 2.41 (1H, dd, *J* = 16.3 & 9.0 Hz, C(2)*H_AH_B*), 1.81-1.60 (1H, m, C(4)*H*), 0.93 (3H, d, *J* = 6.7 Hz, C(4)H(CH₃)_A(CH₃)_B), 0.91 (3H, d, *J* = 6.7 Hz, C(4)H(CH₃)_A(CH₃)_B).

¹H NMR spectroscopic data in good agreement with that of the literature.³⁵

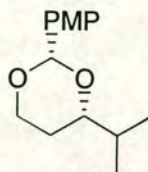
(3*S*)-4-Methylpentane-1,3-diol **159**

To a solution of aldol adduct **156** (270 mg, 0.98 mmol) in THF (10 ml) was added a solution of NaBH₄ (114 mg, 1.71 mmol) in THF (10 ml + 10 drops of H₂O) and the reaction stirred at room temperature for 20 min after which time the bright yellow solution had become colourless. (The reaction whilst being self-indicating was monitored to completion by tlc analysis.) HCl (0.5 M) was added carefully until no more effervescence occurred and the solution extracted with CH₂Cl₂ (3 x 30 ml). The organics were dried (MgSO₄) and the volatiles removed under reduced pressure. Flash chromatography (5% MeOH in EtOAc) afforded the 1,3-diol **159** as a colourless oil (98 mg, 85%) and recovered auxiliary **151** (139 mg, 88%). *R_f* (50% EtOAc in hexane) = 0.14; $[\alpha]_D^{23} = -6.52^\circ$ (*c* 1.31, CHCl₃), lit.¹⁴³ -6.9° (*c* 2.84, CHCl₃); ν_{max} (neat)/cm⁻¹ 3373 (OH); ¹H NMR δ (250 MHz, CDCl₃) 3.92-3.78 (2H, m, CH₂OH), 3.66-3.56 (1H, m, CHOH), 2.63 (1H, br s, OH), 2.47 (1H, br d, *J* = 3.1 Hz, OH), 1.74-1.51 (3H, m, C(4)*H* and C(2)*H*₂), 0.92 (3H, d, *J* = 6.8 Hz, C(4)H(CH₃)_A(CH₃)_B), 0.90 (3H, d, *J* = 6.8 Hz, C(4)H(CH₃)_A(CH₃)_B); ¹³C NMR δ (62.9 MHz, CDCl₃) 77.2 (CH), 62.1 (CH₂), 34.9 (CH₂), 33.9 (CH), 18.3 (CH₃), 17.4 (CH₃); *m/z* (EI) 119 ([M+H]⁺ 1), 100 (4), 75 (100%).

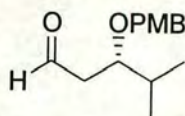
¹H NMR and ¹³C NMR spectroscopic data in good agreement with that of the literature.¹⁴⁴

(3*S*)-4-Methyl-3-*p*-methoxybenzyloxypentanol 161

To a mixture of diol **159** (124 mg, 1.05 mmol) and TsOH.H₂O (15 mg, 0.079 mmol) in DMF (1 ml) was added *p*-methoxybenzylaldehyde dimethyl acetal (287 mg, 1.58 mmol) dropwise. After stirring at room temperature for 10 h the mixture was poured onto NaCl (sat. aq., 5 ml) and extracted with CH₂Cl₂ (3 x 10 ml), the organics were dried (MgSO₄) and the volatiles removed under reduced pressure. The acetal **160** was passed through a small pad of silica eluting (5% EtOAc in CH₂Cl₂) removing the residual DMF to give a clear oil (220 mg, 89%) which was used without further purification in the next step. To a solution of acetal (80 mg, 0.340 mmol) in CH₂Cl₂ (5 ml) at 0 °C was added DIBAL-H (1.02 ml of a 1.0 M solution in toluene, 1.02 mmol) dropwise and stirred at room temperature for 15 min. EtOH was added dropwise very carefully until all the effervescence had ceased. Potassium sodium tartrate tetrahydrate (10 ml; sat.) and CH₂Cl₂ (10 ml) were added and the mixture stirred vigorously until two distinct phases were visible. The layers were separated and the aqueous phase extracted with CH₂Cl₂ (2 x 10 ml). The organics were combined, dried (MgSO₄) and the volatiles removed under reduced pressure. Flash chromatography (EtOAc) afforded **161** as a colourless oil (58 mg, 72%). *R_f* (20% EtOAc in hexane) = 0.19; $[\alpha]_D^{23} = -53.4^\circ$ (*c* 0.89, CHCl₃); ν_{max} (neat)/cm⁻¹ 3409 (OH); ¹H NMR δ (200 MHz, CDCl₃) 7.23-7.16 (2H, m, Ar), 6.84-6.76 (2H, m, Ar), 4.47 (1H, d, *J* = 11.0 Hz, ArCH_AH_B), 4.33 (1H, d, *J* = 11.0 Hz, ArCH_AH_B), 3.73 (3H, s, OCH₃), 3.67 (2H, t, *J* = 5.9 Hz, CH₂OH), 3.35 (1H, dt, *J* = 5.9 & 5.5 Hz, CHOPMB), 2.38 (1H, br s, OH), 2.05-1.89 (1H, m, C(4)*H*), 1.63 (2H, td, *J* = 5.9 & 5.5 Hz, C(2)*H*₂), 0.92 (3H, d, *J* = 6.6 Hz, C(4)H(CH₃)_A(CH₃)_B), 0.90 (3H, d, *J* = 7.0 Hz, C(4)H(CH₃)_A(CH₃)_B); ¹³C NMR δ (50.3 MHz, CDCl₃) 159.2, 130.5, 129.4 (2C), 113.8 (2C), 83.1, 71.0, 61.1, 55.1, 31.4, 29.7, 18.6, 16.8; *m/z* (EI) 238 ([M+H]⁺ 3), 137 (59), 121 (100%).

Intermediate:**(2*S*,4*S*)-4-Isopropyl-2-*p*-methoxyphenyl-1,3-dioxane 160**

Major diastereomer: R_f (10% EtOAc in CH_2Cl_2) = 0.89; $^1\text{H NMR}$ δ (200 MHz, CDCl_3) 7.45-7.38 (2H, m, Ar), 6.92-6.85 (2H, m, Ar), 5.46 (1H, s, PhCH), 4.47 (1H, ddd, $J = 11.4, 5.0$ & 1.1 Hz, C(6) H_AH_B), 3.91 (1H, ddd, $J = 12.4, 11.4$ & 3.0 Hz, C(6) H_AH_B), 3.80 (3H, s, OCH_3), 3.51 (1H, ddd, $J = 11.0, 6.6$ & 2.5 Hz, CHOPMP), 1.91-1.42 (3H, m, C(4) H and C(5) H_2), 0.92 (3H, d, $J = 6.6$ Hz, $\text{CH}(\text{CH}_3)_A(\text{CH}_3)_B$), 0.90 (3H, d, $J = 6.6$ Hz, $\text{CH}(\text{CH}_3)_A(\text{CH}_3)_B$).

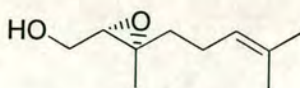
(3*S*)-4-Methyl-3-*p*-methoxybenzyloxypentanal 5

The alcohol **161** (30 mg, 0.126 mmol) was dissolved in THF (500 μl) and added to a clear solution of IBX (53 mg, 0.189 mmol) in DMSO (500 μl) and the solution stirred at room temperature in a stoppered flask under air for 1h. H_2O (3 ml) was added and the white precipitate removed by filtration. The solution was extracted with EtOAc (3 x 20 ml), dried (MgSO_4), the solvent removed under reduced pressure and the resulting oil purified by passing through a small plug of silica (EtOAc) to give the aldehyde **5** as an unstable, colourless oil 28 mg (94%). R_f (20% EtOAc in hexane) = 0.44; $[\alpha]_D^{23} = -65.7^\circ$ (c 0.26, CHCl_3); ν_{max} (neat)/ cm^{-1} 1722 (aldehyde); $^1\text{H NMR}$ δ (200 MHz, CDCl_3) 9.78 (1H, dd, $J = 2.8$ & 1.6 Hz, $\text{HC}=\text{O}$), 7.25-7.11 (2H, m, Ar), 6.89-6.82 (2H, m, Ar), 4.51 (1H, d, $J = 11.0$ Hz, PhCH_AH_B), 4.43 (1H, d, $J = 11.0$ Hz, PhCH_AH_B), 3.79 (3H, s, OCH_3), 3.80-3.69 (1H, m, CHOPMB),

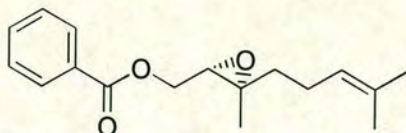
2.62 (1H, ddd, 16.0, 8.1 & 2.8 Hz, C(2) H_AH_B), 2.46 (1H, ddd, 16.0, 3.6 & 1.6 Hz, C(2) H_AH_B), 2.05-1.89 (1H, m, C(4) H), 1.63 (2H, td, J = 5.9 & 5.5 Hz, C(2) H_2), 0.92 (3H, d, J = 6.6 Hz, CH(CH₃)_A(CH₃)_B), 0.90 (3H, d, J = 7.0 Hz, CH(CH₃)_A(CH₃)_B).

¹H NMR in good agreement with that of the literature.¹⁴⁵

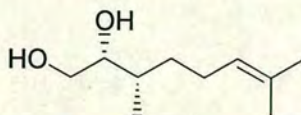
(2*S*,3*S*)-3,7-Dimethyl-2,3-oxiranyl-oct-6-en-1-ol 165



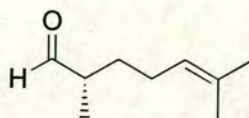
Titanium (IV) isopropoxide (0.91 g, 3.20 mmol) and *L*-(+)-diethyltartrate (1.00 g, 4.84 mmol) were added sequentially to a mixture of dried 4 Å powdered molecular sieves and CH₂Cl₂ (45 ml) at 0 °C. The solution was cooled to -25 °C and 'butyl hydroperoxide (10.4 ml of a 5.0 M solution in decane, 52.0 mmol) was added dropwise. The solution was cooled to -30 °C and geraniol (5.00 g, 32.41 mmol) was added dropwise keeping the reaction between -25 °C and -30 °C. The reaction stirred for a further 1.5 h at -30 °C before the addition of H₂O (25 ml). The mixture was warmed to room temperature and KOH (6 ml, 30% aqueous saturated with NaCl) was then added. The organic layer was separated and the aqueous fraction extracted with CH₂Cl₂ (2 x 50 ml). The organics were combined, dried (MgSO₄), the volatiles removed under reduced pressure and the residual oil purified by kugelrohr distillation to give a colourless oil as **165** (4.03 g, 73%). R_f (20% EtOAc in hexane) = 0.28; BP 92 °C (0.5 mmHg), lit.¹¹⁶ 80 °C (0.4 mmHg); $[\alpha]_D^{23}$ = -5.4° (c 3.0, CHCl₃), lit.¹¹⁶ $[\alpha]_D^{23}$ = -5.89° (c 3.0, CHCl₃); ν_{\max} (neat)/cm⁻¹ 3411 (OH); ¹H NMR δ (200 MHz, CDCl₃) 5.12-5.00 (1H, m, C(6) H), 3.88-3.58 (2H, m, CH₂OH), 2.96 (1H, dd, J = 6.6 & 6.4 Hz, C(2) HO), 2.13-2.01 (2H, m, C(5) H_2), 1.72-1.36 (2H, m, C(4) H_2), 1.67 (3H, s, CH=C(CH₃)_A(CH₃)_B), 1.59 (3H, s, CH=C(CH₃)_A(CH₃)_B), 1.28 (3H, s, C(3)CH₃); ¹³C NMR δ (50.3 MHz, CDCl₃) 132.1, 123.2, 62.9, 61.3, 61.1, 38.3, 25.5, 23.5, 17.5, 16.5.

(2*S*,3*S*)-1-Benzoyl-3,7-dimethyl-2,3-oxiranyl-oct-6-enoate 166

To a solution of **165** (123 mg, 0.722 mmol) in CH_2Cl_2 (5 ml) was added triethylamine (132 μl , 0.939 mmol) followed by benzoyl chloride (109 μl , 0.939 mmol) dropwise at 0 °C. The reaction was stirred for 40 minutes before adding to NH_4Cl (15 ml; sat.). The aqueous phase was extracted with EtOAc (2 x 15 ml), the organics combined, washed with NaCl (40 ml; sat.), dried (MgSO_4) and the volatiles removed under reduced pressure. Flash chromatography (50% CH_2Cl_2 in hexane) afforded the ester **166** as a colourless oil (172 mg, 87%). R_f (20% EtOAc in hexane) = 0.53; **Chiral HPLC** (Chiracel OD column) R_t (5% *i*-PrOH in hexane) 10.2 min (minor enantiomer), 13.7 min (major enantiomer); %ee determined as 88%; ν_{max} (neat)/ cm^{-1} 1720 (C=O); $^1\text{H NMR}$ δ (250 MHz, CDCl_3) 8.09-8.04 (2H, m, Ar), 7.60-7.40 (3H, m, Ar), 5.12-5.00 (1H, m, C(6)*H*), 4.55 (1H, dd, J = 12.1 & 4.4 Hz, $\text{CH}_\text{A}\text{H}_\text{B}\text{OBz}$), 4.28 (1H, dd, J = 12.1 & 6.7 Hz $\text{CH}_\text{A}\text{H}_\text{B}\text{OBz}$), 3.11 (1H, dd, J = 6.7 & 4.4 Hz, C(2)*HO*), 2.14-2.05 (2H, m, C(5) H_2), 1.76-1.41 (2H, m, C(4) H_2), 1.65 (3H, s, $\text{CH}=\text{C}(\text{CH}_3)_\text{X}(\text{CH}_3)_\text{Y}$), 1.59 (3H, s, $\text{CH}=\text{C}(\text{CH}_3)_\text{X}(\text{CH}_3)_\text{Y}$), 1.28 (3H, s, C(3) CH_3); $^{13}\text{C NMR}$ δ (50.3 MHz, CDCl_3) 166.3, 133.0, 132.6, 132.1, 132.0, 129.7, 129.0, 128.2, 123.2, 63.8, 60.5, 59.7, 38.2, 25.5, 23.5, 17.5, 16.8.

(2*R*,3*S*)-3,7-Dimethyloct-6-ene-1,2-diol 167

Sodium cyanoborohydride (6.10 g, 97.06 mmol) was added in one portion to a solution of epoxygeraniol **165** (8.26 g, 48.53 mmol) in THF (200 ml) containing a little bromocresol green at room temperature. $\text{BF}_3 \cdot \text{OEt}_2$ (~6 ml) was added dropwise until the blue solution turned yellow. Further dropwise addition of the Lewis acid was made until the reaction became permanently yellow and the reaction was stirred for a further 2 h. HCl (13 ml; 4 M) was then added dropwise (CARE: HCN evolution) and the reaction stirred for a further 15 min. The mixture was neutralised with 10% aqueous NaOH, extracted with EtOAc (3 x 150 ml), dried (MgSO_4) and the volatiles removed under reduced pressure. Flash chromatography (EtOAc) afforded the diol **167** as a clear, colourless oil (4.98 g, 60%). R_f (50% EtOAc in hexane) = 0.22; $[\alpha]_D^{23} = -4.1^\circ$ (c 0.36, EtOH); ν_{max} (neat)/ cm^{-1} 3370 (OH); $^1\text{H NMR}$ δ (200 MHz, CDCl_3) 5.12-5.02 (1H, m, C(6)*H*), 3.63-3.46 (3H, m, CH_2OH and CHOH), 2.62 (2H, br s, 2 x OH), 2.14-1.84 (2H, m, C(5) H_2), 1.80-1.16 (3H, m, C(3)*H* and C(4) H_2), 1.66 (3H, s, $\text{CH}=\text{C}(\text{CH}_3)_A(\text{CH}_3)_B$), 1.58 (3H, s, $\text{CH}=\text{C}(\text{CH}_3)_A(\text{CH}_3)_B$), 0.90 (3H, d, $J = 6.8$ Hz, C(3) HCH_3); $^{13}\text{C NMR}$ δ (50.3 MHz, CDCl_3) 131.4, 124.3, 75.6, 64.9, 35.1, 32.9, 25.5, 25.3, 17.4, 14.2.

(2*S*)-2,6-Dimethyloct-5-enal (melonal) 79

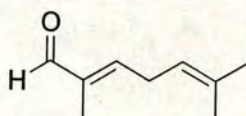
Sodium periodate (3.10 g, 14.50 mmol) was added in one portion to a vigorously stirred mixture of diol **167** (500 mg, 2.27 mmol) in CH_2Cl_2 (17 ml) and pH 7 phosphate buffer (17 ml) and the reaction stirred for 4 h until complete by tlc. The

aqueous phase was extracted with CH_2Cl_2 (3 x 30 ml), the organics combined, dried (Na_2SO_4) and the volatiles removed under reduced pressure⁵. The aldehyde was passed through a small plug of silica (50% EtOAc in hexane) affording **79** as a colourless, unstable, fragrant oil (309 mg, 74%). Chiral shift analysis ^1H NMR studies performed in CDCl_3 at 200 MHz using europium (III) *tris*-[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate, $\text{Eu}(\text{hfc})_3$ indicated 85% ee. R_f (20% EtOAc in hexane) = 0.69; ν_{max} (neat)/ cm^{-1} 2710 (CH, aldehyde), 1726 (C=O); ^1H NMR δ (250 MHz, CDCl_3) 9.60 (1H, d, J = 2.0 Hz, $\text{HC}=\text{O}$), 5.28-5.03 (1H, m, C(5)*H*), 2.33 (1H, qtd, J = 7.0, 6.8 & 2.0 Hz, $\text{CHC}=\text{O}$), 2.06-1.97 (2H, m, C(4)*H*₂), 1.82-1.30 (2H, m, C(3)*H*₂), 1.67 (3H, s, $\text{CH}=\text{C}(\text{CH}_3)_\text{A}(\text{CH}_3)_\text{B}$), 1.58 (3H, s, $\text{CH}=\text{C}(\text{CH}_3)_\text{A}(\text{CH}_3)_\text{B}$), 1.07 (3H, d, J = 7.0 Hz C(2)*HCH*₃); ^{13}C NMR δ (50.3 MHz, CDCl_3) 205.2 (C), 132.6 (C), 123.3 (CH), 45.7 (CH), 31.5 (CH_2), 30.5 (CH_2), 25.6 (CH_3), 25.2 (CH_2), 17.6 (CH_3), 13.2 (CH_3).

A small amount of a UV active LoR_f impurity (5 mg, 2%) as a sharp smelling colourless oil was also isolated. This impurity is thought to have arisen from periodate cleavage of a residual impurity in the starting 1,2-diol.

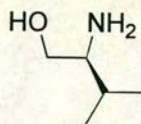
Minor impurity

2,6-Dimethylocta-2,5-dienal **169**



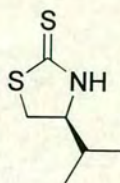
R_f (20% EtOAc in hexane) = 0.61; ^1H NMR δ (200 MHz, CDCl_3) 9.60 (1H, d, J = 1.1 Hz, $\text{HC}=\text{O}$), 6.37 (1H, td, J = 7.4 & 1.1 Hz, C(3)*H*) 5.24-5.05 (1H, m, C(5)*H*), 2.97 (2H, dd, J = 7.4 & 7.0 Hz, C(4)*H*₂), 1.70 (3H, s, $\text{CH}=\text{CCH}_3$), 1.67 (3H, s, $\text{CH}=\text{CCH}_3$), 1.60 (3H, s, $\text{CH}=\text{CCH}_3$).

⁵ The aldehyde is quite volatile and care should be exercised in removing the residual solvent.

(S)-Valinol [(S)-2-Amino-3-methyl-1-butanol] 172

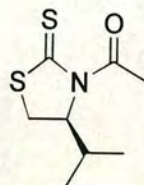
To a stirred mixture of NaBH_4 (26.04 g, 690 mmol) in THF (500 ml) at 0 °C was added *S*-valine (30.00 g, 255 mmol) in one portion. Iodine (64.70 g, 255 mmol) in THF (60 ml + 60 ml washings) was added slowly *via* a dropping funnel. When the yellow hue had subsided (*c.* 20 minutes) the reaction was heated under reflux for 18 h. The mixture was cooled to room temperature and MeOH added carefully and dropwise until a colourless solution was obtained. The volatiles were then removed under reduced pressure to afford a thick paste which was dissolved in KOH (250 ml; 4M) and heated under reflux stirred for a further 15 h. The solution was extracted with CH_2Cl_2 (3 x 750 ml), dried (MgSO_4) and the volatiles removed under reduced pressure. Distillation of the crude product afforded **172** as a viscous, fragrant oil (21.5 g, 81%). BP 78 °C (7 mm Hg), lit.¹⁴² 81 °C (8 mm Hg); $[\alpha]_{\text{D}}^{23} = +14.4^\circ$ (*c* 1.1, EtOH), lit.¹⁴² +18.5° (*c* 7.83, EtOH).

The ^1H NMR spectral data was identical in every respect to that of the enantiomer **150**.

(4*S*)-4-(isopropyl)-2-thiazolidinethione 173

To a solution of *S*-valinol **172** (21.50 g, 208.7 mmol) in KOH (1250 ml, 1250 mmol; 1*N* aqueous), was added carbon disulfide (75.2 ml, 1250 mmol) and the mixture heated under reflux for 30 h. The reaction was cooled to room temperature, extracted with CH₂Cl₂ (3 x 1000 ml), dried (MgSO₄) and the volatiles removed under reduced pressure. The yellow solid was recrystallised from diethyl ether to afford a colourless, crystalline solid as **173** (28.30 g, 84%). **MP** 67-68 °C; $[\alpha]_D^{23} = -20.2^\circ (c\ 8.1, \text{CHCl}_3)$; **HRMS** (CI, NH₃) $[M]^+$ found 161.0333, C₆H₁₁NS₂ requires 161.0333.

Spectral data identical to that of the enantiomer **151**.

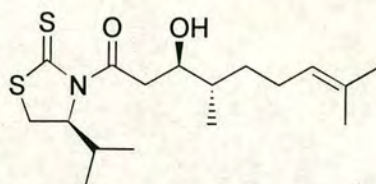
(4*S*)-*N*-Ethanoyl-4-isopropyl-2-thiazolidinethione 171

To a suspension of NaH (60% suspension in mineral oil washed with dry hexane; 8.61 g, 215.3 mmol) in THF (300 ml) was added a solution of *S*-thiazolidinethione **173** (21.20 g, 107.6 mmol) in THF (40 ml + 40 ml washings) at 0 °C and the mixture was stirred at that temperature for 25 min. Acetyl chloride (13.77 ml, 193.7 mmol) was added dropwise and the reaction stirred at 0 °C for a further 1.5 h. The turbid solution was very carefully quenched with H₂O (50 ml) at 0 °C, neutralised with HCl (1*N* aqueous) and extracted with EtOAc (3 x 400 ml). The organic extracts were washed with NaCl (1000 ml; sat.), dried (MgSO₄) and the volatiles removed under

reduced pressure. Flash chromatography (20% EtOAc in hexane) afforded acetate **171** as a bright, yellow oil (21.20 g, 97%). R_f (20% EtOAc in hexane) = 0.49; **Chiral HPLC** (Chiracel OD column) R_t (5% *i*-PrOH in hexane) 20.4 min; $[\alpha]_D^{23} = +459.7^\circ$ (c 0.48, CHCl_3); **HRMS** (CI, NH_3) $[M+H]^+$ found 204.0517, $\text{C}_8\text{H}_{13}\text{NOS}_2$ requires 204.0517.

Spectral data identical to that of the enantiomer **149**.

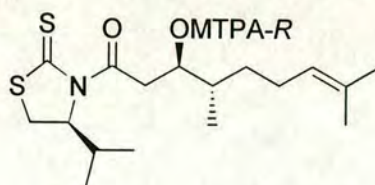
(3'*R*,4*S*,4'*S*)-3-(4',8'-Dimethyl-3'-hydroxy-1'-oxo-non-7'-enyl)-4-(isopropyl)-2-thiazolidinethione 174



To a solution of **171** (942 mg, 4.64 mmol) in CH_2Cl_2 (15 ml) at -78°C was added TiCl_4 (540 μl , 4.91 mmol) dropwise followed by DIPEA (855 μl , 4.91 mmol) dropwise and the deep red reaction mixture stirred for 20 minutes. α -Chiral aldehyde **79** (382 mg, 2.73 mmol) in CH_2Cl_2 (1 ml + 1 ml washings) was added dropwise and the reaction stirred for a further 30 min at -78°C . NH_4Cl (30 ml; sat.) was added and the reaction warmed to room temperature. The aqueous phase was extracted with CH_2Cl_2 (2 x 20 ml), the organics combined, dried (MgSO_4) and the volatiles removed under reduced pressure. Flash chromatography (5% EtOAc in CH_2Cl_2) afforded the aldol adduct as a colourless, bright yellow oil (386 mg, 69%). ^1H NMR analysis showed the oil contained a 6:1 mixture of diastereomers **174** and **175** which proved to be inseparable by HPLC. The absolute stereochemistry of the hydroxy centre of the major diastereomer was confirmed by Mosher ester analysis (see below). **Major** diastereomer: R_f (20% EtOAc in hexane) = 0.30; ν_{max} (neat)/ cm^{-1} 3472 (OH), 1690 ($\text{C}=\text{O}$); ^1H NMR δ (360 MHz, CDCl_3) 5.14 (1H, dd, $J = J' = 7.0$ Hz, C(4)*H*), 5.08 (1H, br t, $J = 6.9$ Hz, C(7')*H*), 3.91 (1H, ddd, $J = 10.0, 5.6$ & 2.0

Hz, C(3')H), 3.55 (1H, dd, $J = 17.7$ & 2.0 Hz, C(2')H_AH_B), 3.50 (1H, dd, $J = 11.2$ & 7.9 Hz, C(5)H_XH_Y), 3.15 (1H, dd, $J = 17.7$ & 10.0 Hz, C(2')H_AH_B), 3.01 (1H, dd, $J = 11.2$ & 0.5 Hz, C(5)H_XH_Y), 2.72 (1H, br s, OH), 2.38-2.30 (1H, m, C(4)CH), 2.14-1.96 (1H, m, C(6')H_CH_D), 2.02-1.85 (1H, m, C(6')H_CH_D), 1.70-1.44 (2H, m, C(4')H and C(5')H_EH_F), 1.67 (3H, s, CH=C(CH₃)_V(CH₃)_W), 1.60 (3H, s, CH=C(CH₃)_V(CH₃)_W), 1.30-1.11 (1H, m, C(5')H_EH_F), 1.05 (3H, d, $J = 6.9$ Hz, C(4)CH(CH₃)_T(CH₃)_U), 0.97 (3H, d, $J = 6.9$ Hz, C(4)CH(CH₃)_T(CH₃)_U), 0.90 (3H, d, $J = 6.8$ Hz, C(4')(CH₃); ¹³C NMR δ (50.3 MHz, CDCl₃) 203.0, 173.4, 131.2, 124.2, 71.2, 71.1, 41.9, 37.3, 32.1, 30.5, 30.3, 25.4, 25.2, 18.7, 17.4, 17.3, 14.6; HRMS (FAB, thioglycerol) [M+H]⁺ found 344.1710, C₁₇H₃₀NO₂S₂ requires 344.1718; m/z 344 ([M+H]⁺ 32), 326 (23), 164 (44), 162 (100%).

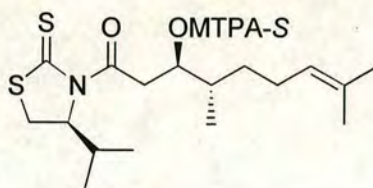
***R*-MTPA ester of (3'*R*,4*S*,4'*S*)-3-(4',8'-Dimethyl-3'-hydroxy-1'-oxo-non-7'-enyl)-4-(isopropyl)-2-thiazolidinethione 177**



To a solution of **174** (50 mg, 0.146 mmol) in THF (3 ml) was added *S*-methoxytrifluoromethylphenylacetic acid (68 mg, 0.292 mmol) in one portion followed by DCC (60 mg, 0.292 mmol) and DMAP (2 mg, cat.). The reaction was stirred for 2 h at room temperature before being diluted with diethyl ether (10 ml) and filtered through a short plug of glass wool. The filtrate was washed with NaHCO₃ (10 ml; sat.) and H₂O (10 ml), dried (MgSO₄) and the volatiles removed under reduced pressure. Flash chromatography (20% EtOAc in hexane) afforded the ester **177** as a colourless, yellow oil (69 mg, 85%). **Major** diastereomer: **R_f** (20% EtOAc in hexane) = 0.48; ¹H NMR δ (250 MHz, CDCl₃) 7.62-7.33 (5H, m, Ar), 5.64 (1H, ddd, $J = 10.3, 4.0$ & 2.2 Hz, C(3')H), 5.06 (1H, br t, $J = 7.3$ Hz, C(7')H), 4.69 (1H, dd, $J = J' = 7.0$ Hz, C(4)H), 3.58 (1H, dd, $J = 17.8$ & 10.3 Hz, C(2')H_AH_B), 3.55 (3H, s, OCH₃), 3.49 (1H, dd, $J = 17.8$ & 9.5 Hz, C(2')H_AH_B), 3.42 (1H, dd, $J =$

11.4 & 7.7 Hz, C(5) H_XH_Y), 2.93 (1H, dd, $J = 11.4$ & 0.6 Hz, C(5) H_XH_Y), 2.41-2.23 (1H, m, C(4)CH), 2.17-1.82 (3H, m, C(6') H_2 and C(4') H), 1.67 (3H, s, CH=C(CH₃)_C(CH₃)_D), 1.63-1.18 (2H, m, C(5') H_2), 1.60 (3H, s, CH=C(CH₃)_C(CH₃)_D), 1.02 (3H, d, $J = 6.8$ Hz, C(4)CH(CH₃)_V(CH₃)_W), 0.94 (3H, d, $J = 6.6$ Hz, C(4')(CH₃), 0.93 (3H, d, $J = 6.8$ Hz, C(4)CH(CH₃)_V(CH₃)_W); **¹H NMR decoupling experiments** δ (250 MHz, CDCl₃) Irradiation at 5.64 led to simplification at 3.58, 3.49 and 2.17-1.82, irradiation at 5.06 led to simplification at 2.17-1.82, irradiation at 4.69 led to simplification at 3.42, 2.93 and 2.41-2.33 and irradiation at 2.37 caused simplification at 4.69, 1.02 and 0.93; **¹⁹F NMR** δ (50.3 MHz, CDCl₃) -71.5.

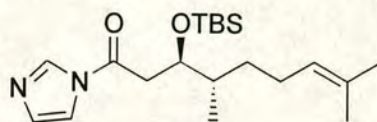
***S*-MTPA ester of (3'*R*,4*S*,4'*S*)-3-(4',8'-Dimethyl-3'-hydroxy-1'-oxo-non-7'-enyl)-4-(isopropyl)-2-thiazolidinethione 178**



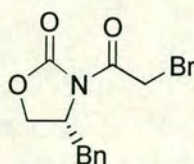
To a solution of **174** (56 mg, 0.160 mmol) in THF (3 ml) was added *S*-methoxytrifluoromethylphenylacetic acid (75 mg, 0.320 mmol) in one portion followed by DCC (66 mg, 0.320 mmol) and DMAP (2 mg, cat.). The reaction was stirred for 2 h at room temperature before being diluted with diethyl ether (10 ml) and filtered through a short plug of glass wool. The filtrate was washed with NaHCO₃ (15 ml; sat.) and H₂O (15 ml), dried (MgSO₄) and the volatiles removed under reduced pressure. Flash chromatography (20% EtOAc in hexane) afforded the ester **178** as a colourless, yellow oil (83 mg, 93%). **Major diastereomer:** R_f (20% EtOAc in hexane) = 0.49; **¹H NMR** δ (250 MHz, CDCl₃) 7.61-7.32 (5H, m, Ar), 5.60 (1H, ddd, $J = 9.5$, 5.6 & 2.0 Hz, C(3') H), 5.04 (1H, br t, $J = 7.3$ Hz, C(7') H), 4.98 (1H, dd, $J = J' = 6.8$ Hz, C(4') H), 3.58 (1H, dd, $J = 18.0$ & 9.5 Hz, C(2') H_AH_B), 3.51 (3H, s, OCH₃), 3.49 (1H, dd, $J = 18.0$ & 2.0 Hz, C(2') H_AH_B), 3.42 (1H, dd, $J = 11.3$ & 8.0 Hz, C(5) H_XH_Y), 3.01 (1H, dd, $J = 11.3$ & 0.5 Hz, C(5) H_XH_Y), 2.43-2.26 (1H,

m, C(4)CH), 2.18-1.80 (3H, m, C(6')H₂ and C(4')H), 1.67 (3H, s, CH=C(CH₃)_C(CH₃)_D), 1.63-1.18 (2H, m, C(5')H₂), 1.58 (3H, s, CH=C(CH₃)_C(CH₃)_D), 1.04 (3H, d, *J* = 7.0 Hz, C(4)CH(CH₃)_V(CH₃)_W), 0.96 (3H, d, *J* = 7.0 Hz, C(4)CH(CH₃)_V(CH₃)_W), 0.80 (3H, d, *J* = 6.6 Hz, C(4')(CH₃); ¹H NMR decoupling experiments δ (250 MHz, CDCl₃) Irradiation at 1.90 led to simplification at 0.80 and irradiation at 0.80 caused simplification at 2.18-1.80, ¹⁹F NMR δ (50.3 MHz, CDCl₃) -71.7.

(3'*R*,4'*S*)-1-(3'-*t*-Butyldimethylsilyloxy-8'-dimethyl-1'-oxo-non-7'-enyl)-imidazole 176



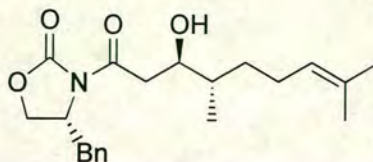
To a solution of aldol adduct **171** (600 mg, 1.75 mmol) in DMF (3 ml) was added TBSCl (528 mg, 3.50 mmol) and imidazole (476 mg, 7.00 mmol) and the reaction stirred at room temperature for 72 h. NaCl (20 ml; sat.) was added and the mixture extracted with EtOAc (3 x 30 ml). The organics were dried (MgSO₄), the volatiles removed under reduced pressure and the residue purified by flash chromatography (2% EtOAc in hexane) to give the imidazole **176** (1.16 g, 91%) still as a mixture of diastereomers. *R_f* (20% EtOAc in hexane) = 0.28; ¹H NMR δ (200 MHz, CDCl₃) 8.15 (1H, s, Ar), 7.49 (1H, d, *J* = 1.5 Hz, Ar), 7.07 (1H, d, *J* = 1.5 Hz, Ar), 5.07 (1H, br t, *J* = 7.0 Hz, C(H)), 4.21 (1H, ddd, *J* = 9.5, 3.7 & 2.9 Hz, CHOTBS), 2.95 (1H, dd, *J* = 13.9 & 9.5 Hz, C(2')H_AH_B), 2.64 (1H, dd, *J* = 13.9 & 2.9 Hz, C(2')H_AH_B), 2.08-1.84 (2H, m, C(6')H₂), 1.81-1.10 (3H, m, C(4')H and C(5')H₂), 1.68 (3H, s, CH=C(CH₃)_A(CH₃)_B), 1.61 (3H, s, CH=C(CH₃)_A(CH₃)_B), 0.96 (3H, d, *J* = 6.6 Hz, C(4')HCH₃), 0.74 (9H, s, *t*-BuSi), -0.01 (3H, s, SiMe), -0.22 (3H, s, SiMe); ¹³C NMR δ (50.3 MHz, CDCl₃) 168.9, 136.6, 132.4, 130.8, 123.9, 116.2, 73.1, 38.4, 37.8 (2C), 25.5 (4C), 25.4 (2C), 17.6, 13.0, -5.3 (2C).

(4*R*)-3-(2'-Bromo-1'-oxo-ethanyl)-4-(phenylmethyl)-2-oxazolidinone 186

To a solution of *R*-imide **185** (3.20 g, 18.08 mmol) in THF (60 ml) was added ⁿBuLi (11.9 ml of a 1.52 M solution in hexane, 18.08 mmol) followed by bromoacetyl bromide (1.73 ml, 19.88 mmol) dropwise at -78 °C. The reaction was stirred at -78 °C for 20 min before being quenched by the addition of NH₄Cl (50 ml; sat.). The THF was removed under reduced pressure, the residue extracted with CH₂Cl₂ (3 x 100 ml), dried (Na₂SO₄) and the volatiles removed under reduced pressure. Flash chromatography (CH₂Cl₂) afforded a yellow oil which, after trituration with hexane, was recrystallised from diethyl ether to give **186** as a colourless, relatively unstable, crystalline solid (3.82 g, 71%). **MP** 40-41 °C, lit.¹²⁶ [α]_D²³ = -74.8° (*c* 2.50, CH₂Cl₂), lit.¹²⁶ +75.4° (*c* 8.0, CHCl₃)[‡]; ν_{max} (neat)/cm⁻¹ 1793 (C=O, imide), 1712 (C=O); ¹H NMR δ (600 MHz, CDCl₃) 7.36-7.15 (5H, m, Ar), 4.73-4.68 (1H, m, C(4)*H*), 4.55 (1H, d, *J* = 12.8 Hz, C(2')*H*_A*H*_BBr), 4.52 (1H, d, *J* = 12.8 Hz, C(2')*H*_A*H*_BBr), 4.28 (1H, dd, *J* = 11.7 & 9.5 Hz, C(5)*H*_X*H*_Y), 4.23 (1H, dd, *J* = 11.7 & 2.9 Hz, C(5)*H*_X*H*_Y), 3.32 (1H, dd, *J* = 13.2 & 3.7 Hz, CH_V*H*_WPh), 2.81 (1H, dd, *J* = 13.2 & 9.5 Hz, CH_V*H*_WPh); ¹³C NMR δ (50.3 MHz, CDCl₃) 165.6, 152.7, 134.5, 129.1 (2C), 128.7 (2C), 127.2, 66.4, 55.0, 37.0, 28.2; **m/z** (FAB) 300 ([M+H]⁺; ⁸¹Br 84), 298 ([M+H]⁺; ⁷⁹Br 100), 178 (57), 91 (66), 77 (51%).

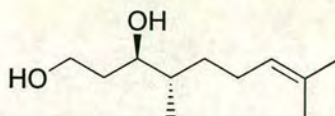
[‡] The optical rotation in the original Evans paper has a sign error.¹⁴⁶

(3'*R*,4*R*,4'*S*)-3-(4',8'-Dimethyl-3'-hydroxy-1'-oxo-non-7'-enyl)-4-(phenylmethyl)-2-oxazolidinone **187**

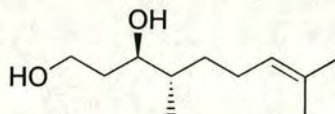


[†] To a suspension of CrCl₂ (2.54 g, 20.67 mmol) and LiI (106 mg, 0.79 mmol) in THF (35 ml) was added **186** (3.08 g, 10.34 mmol) in THF (5 ml + 5 ml washings) followed by the aldehyde in THF (5 ml + 5 ml washings) and the reaction stirred at room temperature for 3 h until no aldehyde remained by tlc. NaCl (50 ml; sat.) was added and the reaction mixture stirred vigorously for 15 min. The aqueous phase was extracted with diethyl ether (2 x 50 ml), the organics combined, dried (MgSO₄) and the volatiles removed under reduced pressure. Flash chromatography (10% EtOAc in CH₂Cl₂) afforded a colourless oil (1.78 g, 62%). ¹H NMR analysis showed the oil contained a 7:1 mixture of diastereomers **187** and **188**. Major diastereomer: *R_f* (50% EtOAc in hexane) = 0.72; ν_{\max} (neat)/cm⁻¹ 3501 (OH), 1781 (C=O, imide), 1690 (C=O); ¹H NMR δ (600 MHz, CDCl₃) 7.45- 7.19 (5H, m, Ar), 5.12-5.08 (1H, m, C(7')H), 4.73-4.67 (1H, m, C(4)H), 4.23 (1H, dd, *J* = 11.8 & 9.5 Hz, C(5)*H_AH_B*), 4.18 (1H, dd, *J* = 11.8 & 2.8 Hz, C(5)*H_AH_B*), 3.98-3.93 (1H, m, CHOH), 3.28 (1H, dd, *J* = 13.5 & 3.4 Hz, CH_XH_YPh), 3.08-3.06 (2H, m, C(2')H₂), 2.93 (1H, d, *J* = 4.8 Hz, OH), 2.80 (1H, dd, *J* = 13.5 & 9.4 Hz, CH_XH_YPh), 2.14-2.03 (1H, m, C(6')H_CH_D), 2.01-1.92 (1H, m, C(6')H_CH_D), 1.70-1.65 (1H, m, C(4')H), 1.67 (3H, s, CH=C(CH₃)_V(CH₃)_W), 1.60 (3H, s, CH=C(CH₃)_V(CH₃)_W), 1.58-1.50 (1H, m, C(5')H_EH_F), 1.26-1.17 (1H, m, C(5')H_EH_F), 0.95 (3H, d, *J* = 6.8 Hz, C(4')(CH₃); All ¹H NMR assignments confirmed by 2D COSY at 600MHz; ¹³C NMR δ (50.3 MHz, CDCl₃) 173.3, 153.4, 134.9, 131.4, 129.3 (2C), 128.8 (2C), 127.3, 124.3, 71.7, 66.1, 54.9, 39.0, 37.7, 37.5, 32.1, 25.5, 25.3, 17.4, 14.6; HRMS (FAB, NOBA) [M+H]⁺ found 360.2162, C₂₁H₃₀O₄N requires 360.2174; *m/z* 360 ([M+H]⁺ 20), 342 (28), 178 (84), 165 (58), 91 (80%).

[†] This reaction must be performed under strictly anhydrous conditions.

(3*R*,4*S*)-4,8-Dimethyl-non-7-en-1,3-diol 189

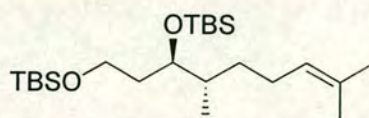
To a solution of aldol adduct **174** (168 mg, 0.49 mmol) in THF (3 ml) was added a solution of NaBH₄ (65 mg, 1.71 mmol) in THF (5 ml + 5 drops of H₂O) and the reaction stirred at room temperature until the solution turned from yellow to colourless (the reaction whilst being self-indicating was monitored to completion by tlc analysis). HCl (0.5 M) was added dropwise until no more effervescence occurred and the solution extracted with CH₂Cl₂ (3 x 20 ml), the organics were dried (MgSO₄) and the volatiles removed under reduced pressure. Flash chromatography (EtOAc) afforded the 1,3-diol **189** as a colourless oil 168 mg (86%).

(3*R*,4*S*)-4,8-Dimethyl-non-7-en-1,3-diol 189

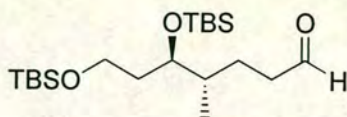
To a solution of aldol adduct **187** (1.75 g, 4.87 mmol) in THF (50 ml) at 0 °C was added LiBH₄ (318 mg, 14.61 mmol) portionwise. The reaction was stirred at room temperature 2.5 h, until complete as judged by tlc, before being quenched by the careful addition of NH₄Cl (100 ml). The mixture was extracted with EtOAc (2 x 100 ml), dried (MgSO₄) and the volatiles removed under reduced pressure. Careful flash chromatography (80%EtOAc in hexane) afforded the 1,3-diol **189** as a colourless oil (628 mg, 69%). *R*_f (EtOAc) = 0.64; [α]_D²³ = -12.1° (*c* 0.81, CHCl₃); ν_{max} (neat)/cm⁻¹ 3369 (OH); ¹H NMR δ (200 MHz, CDCl₃) 5.06 (1H, br t, *J* = 7.0 Hz, C(7)*H*), 3.84-3.62 (3H, m, CH₂OH and CHOH), 3.38 (1H, br s, OH), 2.08-1.80 (2H, m, C(6)*H*₂), 1.71-1.05 (5H, m, C(4)*H*, C(2)*H*₂ and C(5)*H*₂), 1.64 (3H, s, CH=C(CH₃)_A(CH₃)_B), 1.56 (3H, s, CH=C(CH₃)_A(CH₃)_B), 0.86 (3H, d, *J* = 7.0 Hz, C(4)HCH₃); ¹³C NMR δ

(50.3 MHz, CDCl_3) 131.3, 124.4, 75.6, 61.5, 38.4, 33.9, 32.1, 25.4 (2C), 17.4, 14.5; **HRMS** (EI) $[\text{M}]^+$ found 186.1616, $\text{C}_{11}\text{H}_{22}\text{O}_2$ requires 186.1620; **m/z** (EI) 186 ($[\text{M}]^+$ 11), 115 (17), 82 (100%).

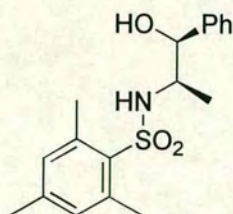
(3*R*,4*S*)-4,8-Dimethyl-1,3-di-*t*-butyldimethylsilyloxy-non-7-ene 190



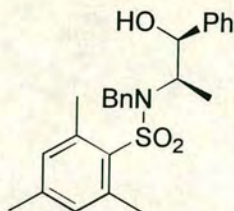
To a solution of diol **189** (548 mg, 2.95 mmol) in CH_2Cl_2 (10 ml) at 0 °C was added 2,6-lutidine (1.37 ml, 11.80 mmol) followed after 5 minutes by *t*-butyldimethylsilyl triflate (2.03 ml, 8.84 mmol) dropwise and the reaction mixture was stirred at 0 °C for 1.5 h. The reaction mixture was diluted with CH_2Cl_2 (50 ml), washed with NaHCO_3 (50 ml; sat.), NaCl (50 ml; sat.), dried (MgSO_4) and the volatiles removed under reduced pressure. Flash chromatography (2% EtOAc in hexane) afforded **190** as a colourless oil (1.16 g, 95%). R_f (1% EtOAc in hexane) = 0.20; $[\alpha]_D^{23} = +20.7^\circ$ (c 1.10, CHCl_3); $^1\text{H NMR}$ δ (600 MHz, CDCl_3) 5.09 (1H, br t, $J = 7.0$ Hz, C(7)*H*), 3.74-3.65 (2H, m, $\text{CH}_\text{A}\text{H}_\text{B}\text{OTBS}$ and CHOTBS), 3.65-3.58 (1H, m, $\text{CH}_\text{A}\text{H}_\text{B}\text{OTBS}$), 2.06-1.98 (1H, m, C(6)*H*_X*H*_Y), 1.97-1.89 (1H, m, C(6)*H*_X*H*_Y), 1.68 (3H, s, $\text{CH}=\text{C}(\text{CH}_3)_\text{C}(\text{CH}_3)_\text{D}$), 1.63-1.50 (3H, m, C(4)*H* and C(5)*H*₂), 1.60 (3H, s, $\text{CH}=\text{C}(\text{CH}_3)_\text{C}(\text{CH}_3)_\text{D}$), 1.33-1.25 (1H, m, C(2)*H*_V*H*_W), 1.17-1.10 (1H, m, C(2)*H*_V*H*_W), 0.88 (9H, s, *t*-BuSi), 0.87 (9H, s, *t*-BuSi), 0.85 (3H, d, $J = 6.8$ Hz, C(4)*HCH*₃), 0.04 (6H, s, 2 x SiMe), 0.02 (3H, s, SiMe), 0.01 (3H, s, SiMe); $^{13}\text{C NMR}$ δ (50.3 MHz, CDCl_3) 131.2, 124.7, 72.1, 60.4, 38.1, 34.6, 32.9, 25.9 (3C), 25.8 (2C), 25.6 (3C), 18.0, 17.6, 13.9 (2C), -4.6, -4.8, -5.4 (2C); **HRMS** (FAB, NOBA) $[\text{M}]^+$ found 414.3344, $\text{C}_{23}\text{H}_{50}\text{O}_2\text{Si}_2$ requires 414.3349; **m/z** 414 ($[\text{M}]^+$ 1), 357 (11), 301 (5), 189 (23), 133 (64%).

(4*S*,5*R*)-5,7-Di-*t*-butyldimethylsilyloxy-4-methyl-heptanal 4

To a solution of **190** (1.16 g, 2.80 mmol) in $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (80 ml; 3:1) was added a few drops of pyridine and Sudan III indicator (5 mg). The red solution was cooled to 78°C and ozone was bubbled through the solution for 30 min until complete as judged by the now yellow colour. The reaction flask was flushed with argon for 5 min before adding dimethyl sulfide (STENCH) (4.11 ml, 56.00 mmol) dropwise. The reaction mixture was allowed to warm to room temperature before removing the volatiles under reduced pressure. The residue was diluted with diethyl ether (100 ml) and hexane (100 ml), washed with NaCl (150 ml; sat.), dried (Na_2SO_4) and the solvent removed under reduced pressure. Flash chromatography (10% EtOAc in hexane) afforded the aldehyde **4** as a clear, colourless, unstable oil (743 mg, 68%). R_f (20% EtOAc in hexane) = 0.63; $[\alpha]_D^{23} = +12.04^\circ$ (c 1.96, CHCl_3); ν_{max} (neat)/ cm^{-1} 2714 (CH, aldehyde), 1727 (C=O); $^1\text{H NMR}$ δ (200 MHz, CDCl_3) 9.76 (1H, t, $J = 0.9$ Hz, HC=O), 5.28-5.03 (1H, m, C(7)*H*), 3.79-3.55 (3H, m, CH_2OTBS and CHOTBS), 2.58-3.0 (1H, m, $\text{CH}_2\text{C=O}$), 1.72-1.20 (5H, m, C(4)*H*, C(2)*H*₂ and C(6)*H*₂), 0.88 (9H, s, *t*-BuSi), 0.87 (9H, s, *t*-BuSi), 0.86 (3H, d, $J = 8.0$ Hz, C(4)*HCH*₃), 0.03 (6H, s, 2 x SiMe), 0.02 (3H, s, SiMe), 0.00 (3H, s, SiMe); $^{13}\text{C NMR}$ δ (50.3 MHz, CDCl_3) 202.5, 71.9, 59.9, 41.9, 37.9, 35.1, 25.8 (6C) 24.5, 18.1, 17.9, 14.2, -4.7 (2C), -5.5 (2C).

(1*S*,2*R*)-2-(*N*-mesitylenesulfonylamino)-1-phenylpropan-1-ol 193

To a solution of 1*S*,2*R*-(+)-norephedrine (7.00 g, 46.30 mmol) and triethylamine 8.43 ml, 55.60 mmol) in CH₂Cl₂ (200 ml) was added mesitylenesulfonyl chloride (10.13 g, 46.39 mmol) at 0 °C. The reaction was stirred at that temperature for 2 h and diluted with ether (400 ml) before being washed sequentially with H₂O (400 ml), HCl (400 ml; 1 N), H₂O (400 ml), NaHCO₃ (400 ml; sat.) and NaCl (400 ml; sat.). The organics were dried (MgSO₄), the volatiles removed under reduced pressure and the solid residue was recrystallised from CH₂Cl₂/hexane to afford **193** as a colourless, crystalline solid (14.50 g, 84%). *R_f* (50% EtOAc in hexane) = 0.63; $[\alpha]_D^{23} = +11.80^\circ$ (*c* 2.09, CHCl₃), lit.²⁷ +12.8° (*c* 2.12, CHCl₃); **MP** 120-121 °C, lit.²⁷ 120.5-121.5 °C; ν_{max} (neat)/ cm⁻¹ 3020 (OH), 1218 (S=O); **¹H NMR** δ (200 MHz, CDCl₃) 7.38-7.20 (5H, m, Ar), 6.96 (2H, s, Ar), 4.96 (1H, br d, *J* = 8.8 Hz, NH), 4.76 (1H, d, *J* = 2.9 Hz, CHOH), 3.59-3.41 (1H, m, C(2)*H*), 2.65 (6H, s, 2 x CH₃Ar), 2.30 (3H, s, CH₃Ar), 0.85 (3H, d, *J* = 6.6 Hz, C(2)HCH₃); **HRMS** (CI, NH₃) [M+H]⁺ found 334.1477, C₁₈H₂₄NO₃S requires 334.1477; **m/z** 334 ([M+H]⁺ 5), 316 (4), 136 (21%). **¹H NMR** spectroscopic data in good agreement with that of the literature.²⁷

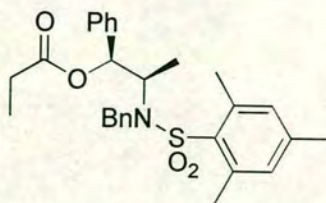
(1*S*,2*R*)-2-(*N*-Benzyl-*N*-mesitylenesulfonylamino)-1-phenylpropan-1-ol **194**

To a solution of **193** (5.12 g, 15.37 mmol) in DMF (70 ml) was added potassium *t*-butoxide (1.73 g, 15.37 mmol) at 0 °C. The reaction was stirred for 30 min, benzyl bromide (1.83 ml, 15.37 mmol) was added and the reaction stirred for a further 4.5 h at room temperature. NaCl (100 ml; sat.) was added and the mixture extracted with CH₂Cl₂ (2 x ml) and EtOAc (200 ml). The organics were combined, dried (MgSO₄), and the residue purified by flash chromatography (20% EtOAc in hexane) to give **194** as a colourless, crystalline solid (6.59, 81%). *R_f*(20EtOAc in hexane) = 0.40; [α]_D²³ = +8.16° (*c* 2.07, CHCl₃), lit.²⁷ +6.43° (*c* 2.05, CHCl₃); **MP** 122-124 °C, lit.²⁷ 123-124 °C; ν_{max} (neat)/ cm⁻¹ 3022 (OH), 1219 (S=O); ¹H NMR δ (200 MHz, CDCl₃) 7.38-7.12 (8H, m, Ar), 7.08-7.02 (2H, m, Ar), 6.94 (2H, s, Ar), 5.02-4.96 (1H, m, CHOH), 4.79 (1H, d, *J* = 16.1 Hz, CH_AH_BPh), 4.56 (1H, d, *J* = 16.1 Hz, CH_AH_BPh), 3.82 (1H, qd, *J* = 7.0 & 1.9 Hz C(2)*H*), 2.65 (6H, s, 2 x CH₃Ar), 2.30 (3H, s, CH₃Ar), 2.18 (1H, d, *J* = 3.4 Hz, OH), 1.03 (3H, d, *J* = 7.0 Hz, C(2)HCH₃); **HRMS** (CI, NH₃) [*M*+*H*]⁺ found 424.1946, C₂₅H₃₀NO₃S requires 424.1946; *m/z* 424 ([*M*+*H*]⁺ 50), 406 (14), 132 (100%).

¹H NMR and ¹³C NMR spectroscopic data in good agreement with that of the literature.²⁷

(1'*S*,2'*R*)-2'-(*N*-Benzyl-*N*-mesitylenesulfonylamino)-1'-phenylpropyl propionate

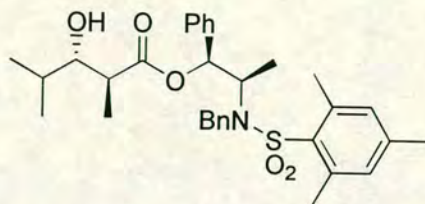
191



To a solution of **194** (2.61 g, 6.17 mmol) in CH_2Cl_2 (30 ml) was added pyridine (699 μl , 8.64 mmol) followed by propionyl chloride (697 μl , 8.02 mmol) at 0 °C. The reaction was stirred for 18 h and then diluted with ether (80 ml) before being washed sequentially with H_2O (100 ml), HCl (100 ml; 1 N), H_2O (100 ml), NaHCO_3 (100 ml; sat.) and NaCl (100 ml; sat.). The organics were dried (MgSO_4), the volatiles removed under reduced pressure and the solid residue was recrystallised from EtOAc/hexane to afford **191** as a colourless, crystalline solid (2.68 g, 91%). R_f (20% EtOAc in hexane) = 0.56; $[\alpha]_D^{23} = -10.36^\circ$ (c 2.47, CHCl_3), lit.²⁷ -11.2° (c 2.38, CHCl_3); **MP** 146-148 °C, lit.²⁷ 147-148 °C; ν_{max} (neat)/ cm^{-1} 1746 (C=O); $^1\text{H NMR}$ δ (200 MHz, CDCl_3) 7.37-7.17 (8H, m, Ar), 6.95-6.90 (4H, m, Ar), 5.85 (1H, d, $J = 3.7$ Hz, C(1')*HO*), 4.74 (1H, d, $J = 16.6$ Hz, $\text{CH}_\text{A}\text{H}_\text{B}\text{Ph}$), 4.62 (1H, d, $J = 16.6$ Hz, $\text{CH}_\text{A}\text{H}_\text{B}\text{Ph}$), 4.04 (1H, qd, $J = 7.0$ & 4.0 Hz C(2')*H*), 2.53 (6H, s, 2 x CH_3Ar), 2.28 (3H, s, CH_3Ar), 2.20-2.04 (2H, m, C(O) CH_2CH_3), 1.12 (3H, d, $J = 7.0$ Hz, C(2')*H*(CH_3), 1.01 (3H, t, $J = 7.7$ Hz, C(O) CH_2CH_3); $^{13}\text{C NMR}$ δ (50.3 MHz, CDCl_3) 172.2, 142.2, 140.0 (2C), 138.6, 138.5, 133.2, 132.0 (2C), 128.3 (4C), 127.7, 127.2 (2C), 126.9, 125.8 (2C), 77.8, 56.1, 47.9, 27.2, 22.8 (2C), 20.6, 12.4, 8.6; **m/z** (FAB, NOBA) 480 ($[\text{M}+\text{H}]^+$ 5), 406 (36), 316 (25), 154 (100), 136 (78%).

$^1\text{H NMR}$ and $^{13}\text{C NMR}$ spectroscopic data in good agreement with that of the literature.²⁷

2'-(*N*-Benzyl-*N*-mesitylenesulfonylamino)-1'-phenylpropyl (1'*S*,2*S*,2'*R*,3*S*)-2,4-dimethyl-3-hydroxypentanoate **196**

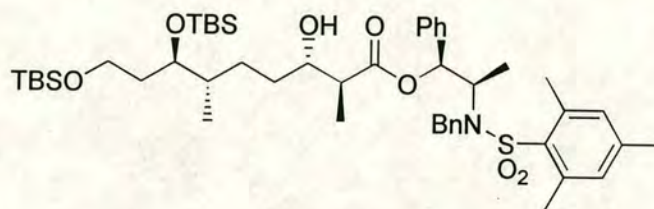


To a stirred solution of **191** (148 mg, 0.309 mmol) in CH_2Cl_2 (4 ml) was added DIPEA (161 μl , 0.927 mmol) at room temperature and the reaction cooled to -78°C . Dicyclopentylboron triflate (1.24 ml of a 0.5 M solution in CH_2Cl_2 , 0.618 mmol) was added dropwise and the reaction mixture stirred for 2 h. Isobutyraldehyde (34 μl , 0.371 mmol) was added and the reaction stirred for a further 1 h followed by 1 h at 0°C . The reaction was quenched by the addition of pH 7 phosphate buffer (4 ml), MeOH (10 ml) and H_2O_2 (1 ml; 30% aqueous) dropwise and stirred vigorously at 0°C for 2 h. H_2O (15 ml) was added and the mixture was extracted with CH_2Cl_2 (3 x 20 ml). The combined organic extracts were washed with NaHCO_3 (30 ml; sat.) and NaCl (30 ml; sat.), dried (MgSO_4) concentrated under reduced pressure to give the crude aldol product. Crude 200 MHz ^1H NMR showed the presence of residual starting material and the aldol adduct as a single diastereomer ($\geq 95:5$). The residue was purified by flash chromatography (25% EtOAc in hexane) to give recovered starting material (58 mg, 39%) and the *anti* aldol adduct **196** as a colourless solid (96 mg, 56%). R_f (20% EtOAc in hexane) = 0.27; $[\alpha]_D^{23} = -19.4^\circ$ (c 1.40, CHCl_3), lit.²⁷ -19.9° (c 1.40, CHCl_3); MP $140\text{--}142^\circ\text{C}$, lit.²⁷ $142\text{--}142.5^\circ\text{C}$; ^1H NMR δ (200 MHz, CDCl_3) 7.38–7.14 (8H, m, Ar), 6.92–6.81 (2H, m, Ar), 6.88 (2H, s, Ar), 5.82 (1H, d, $J = 4.0$ Hz, $\text{C}(1')\text{HO}$), 4.81 (1H, d, $J = 16.5$ Hz, $\text{CH}_\text{A}\text{H}_\text{B}\text{Ph}$), 4.56 (1H, d, $J = 16.5$ Hz, $\text{CH}_\text{A}\text{H}_\text{B}\text{Ph}$), 4.04 (1H, qd, $J = 7.0$ & 4.4 Hz $\text{C}(2')\text{H}$), 3.41 (1H, ddd, $J = 7.2$, 6.2 & 4.4 Hz, $\text{C}(3)\text{H}$), 2.62 (1H, qd \equiv qn, $J = 7.2$ Hz, $\text{C}(2)\text{H}$), 2.50 (6H, s, 2 x CH_3Ar), 2.45 (1H, d, $J = 6.2$ Hz, OH), 2.29 (3H, s, CH_3Ar), 1.82–1.64 (1H, m, $\text{C}(4)\text{H}$), 1.18 (3H, d, $J = 7.2$ Hz, $\text{C}(2)\text{H}(\text{CH}_3)$), 1.11 (3H, d, $J = 7.0$ Hz, $\text{C}(2')\text{H}(\text{CH}_3)$), 0.96 (3H, d, $J = 6.9$ Hz, $\text{C}(4)\text{H}(\text{CH}_3)_\text{C}(\text{CH}_3)_\text{D}$), 0.90 (3H, d, $J = 6.6$ Hz, $\text{C}(4)\text{H}(\text{CH}_3)_\text{C}(\text{CH}_3)_\text{D}$); ^{13}C

NMR δ (62.9 MHz, CDCl_3) 174.9 (C), 142.4 (C), 140.1 (2C), 138.4 (C), 138.0 (C), 133.2 (C), 132.0 (2CH), 128.3 (2CH), 128.2 (2CH), 127.8 (CH), 127.5 (2CH), 127.0 (CH), 125.8 (2CH), 78.0 (CH), 77.5 (CH), 56.6 (CH), 48.1 (CH_2), 42.8 (CH), 30.0 (CH), 22.8 (2 CH_3), 20.7 (CH_3), 19.8 (CH_3), 15.4 (CH_3), 14.2 (CH_3), 13.4 (CH_3).

^1H NMR and ^{13}C NMR spectroscopic data in good agreement with that of the literature.²⁷

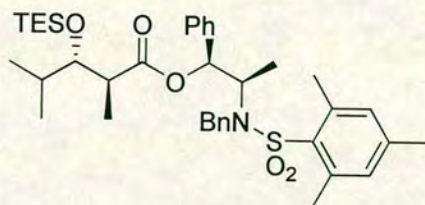
**2'-(*N*-Benzyl-*N*-mesitylenesulfonylamino)-1'-phenylpropyl
(1'*S*,2*S*,2'*R*,3*S*,6*S*,7*R*)-7,9-di-*t*-butyldimethylsilyloxy-2,6-dimethyl-3-
hydroxynonanoate **197****



To a stirred solution of **191** (2.62 g, 5.48 mmol) in CH_2Cl_2 (30 ml) was added DIPEA (161 μl , 0.927 mmol) at -78°C followed by dicyclopentylboron triflate (21.9 ml of a 0.5 M solution in CH_2Cl_2 , 10.96 mmol) dropwise and the reaction mixture stirred for 2 h. Aldehyde **4** (532 mg, 1.37 mmol) was added and the reaction stirred for a further 1.5 h followed by 1.5 h at 0°C . The reaction was quenched by the addition of pH 7 phosphate buffer (16 ml), MeOH (40 ml) and H_2O_2 (4 ml; 30% aqueous) dropwise and stirred vigorously at 0°C for 2 h. H_2O (60 ml) was added and the mixture was extracted with CH_2Cl_2 (3 x 80 ml). The combined organic extracts were washed with NaHCO_3 (150 ml; sat.) and NaCl (150 ml; sat.), dried (MgSO_4) concentrated under reduced pressure to give the crude aldol product. Crude 200 MHz ^1H NMR showed the presence of residual aldehyde and the aldol adduct. The residue was purified by flash chromatography (15% EtOAc in hexane) to give recovered aldehyde **4** (119 mg, 22%) and the *anti* aldol adduct **197** as a colourless, hygroscopic foam (669 mg, 51%). Analysis of the 600 MHz ^1H NMR showed this to be a 6:1 mixture of diastereomers. R_f (20% EtOAc in hexane) = 0.51; $[\alpha]_D^{23} = -17.9^\circ$ (c 0.48,

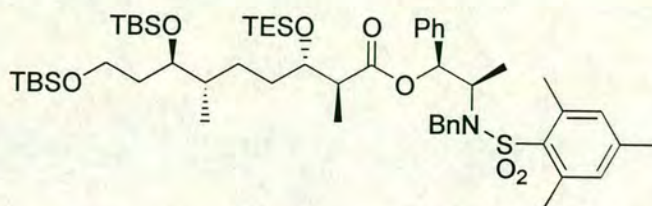
CHCl₃); ν_{\max} (neat)/ cm⁻¹ 3443 (OH), 1732 (C=O); **Major diastereomer**: ¹H NMR δ (600 MHz, CDCl₃) 7.30-7.18 (8H, m, Ar), 6.90-6.87 (4H, m, Ar), 5.83 (1H, d, J = 4.0 Hz, C(1')HO), 4.74 (1H, d, J = 16.5 Hz, CH_AH_BPh), 4.53 (1H, d, J = 16.5 Hz, CH_AH_BPh), 4.13 (1H, qd, J = 7.0 & 4.5 Hz C(2')H), 3.71-3.64 (2H, m, C(7)HOTBS and C(9)H_YH_ZOTBS), 3.62-3.55 (2H, m, C(3)HOH and C(9)H_YH_ZOTBS), 2.49 (6H, s, 2 x CH₃Ar), 2.44 (1H, d, J = 5.8 Hz, OH), 2.42 (1H, dq, J = 7.5 & 7.2 Hz, C(2)H), 2.29 (3H, s, CH₃Ar), 1.62-1.53 (3H, m, C(6)HCH₃ and C(5)H₂), 1.47-1.41 (2H, m, C(4)H₂), 1.40-1.33 (1H, m, C(8)H_CH_D), 1.32-1.25 (1H, m, C(8)H_CH_D), 1.19 (3H, d, J = 7.0 Hz, C(2')H(CH₃), 1.13 (3H, d, J = 7.2 Hz, C(2)H(CH₃), 0.89 (9H, s, *t*-BuSi), 0.88 (9H, s, *t*-BuSi), 0.85 (3H, d, J = 6.9 Hz, C(6)HCH₃), 0.04 (6H, s, 2 x SiMe), 0.03 (3H, s, SiMe), 0.02 (3H, s, SiMe); ¹H NMR decoupling experiments δ (600 MHz, CDCl₃) Irradiation at 2.42 led to simplification at 3.62-3.55 and 1.13, irradiation at 1.43 led to simplification at 3.62-3.55 and 1.62-1.53, irradiation at 1.19 led to simplification at 4.13 and irradiation at 1.13 caused simplification at 2.42; ¹³C NMR δ (62.9 MHz, CDCl₃) 174.5 (C), 142.4 (C), 140.1 (2 x C), 138.3 (C), 138.0 (C), 133.2 (C), 132.0 (2 x CH), 128.3 (2 x CH), 128.2 (2 x CH), 127.9 (CH), 127.5 (2 x CH), 127.1 (CH), 125.9 (2 x CH), 78.1 (CH), 77.4 (CH), 73.0 (CH), 60.3 (CH₂), 56.6 (CH), 48.1 (CH₂), 45.5 (CH), 38.6 (CH), 34.8 (CH₂), 32.2 (CH₂), 28.1 (CH₂), 25.8 (3 x CH₃), 25.7 (3 x CH₃), 22.8 (2 x CH₃), 20.8 (CH₃), 18.2 (C), 18.0 (C), 14.0 (CH₃), 13.9 (CH₃), 13.4 (CH₃), -4.5 (CH₃), -4.7 (CH₃), -5.4 (2 x CH₃); **HRMS** (FAB, NOBA) [M+H]⁺ found 868.5046, C₄₈H₇₈NO₇SSi₂ requires 868.5038; **m/z** 868 ([M+H]⁺ 1), 685 (8), 406 (62), 223 (33), 134 (76%).

2'-(*N*-Benzyl-*N*-mesitylenesulfonylamino)-1'-phenylpropyl (1'*S*,2*S*,2'*R*,3*S*)-2,4-dimethyl-3-triethylsilyloxypentanoate **199**



To a solution of alcohol **196** (45 mg, 0.082 mmol) in DMF (0.5 ml) was added imidazole (22 mg, 0.328 mmol) followed by TESCl (24.7 mg, 0.164 mmol) and the reaction mixture stirred for 18 h at room temperature until complete as followed by tlc. NaCl (2 ml; sat.) was added and the mixture extracted with EtOAc (3 x 5 ml). The organics were dried (MgSO₄), the volatiles removed under reduced pressure and the residue purified by flash chromatography (10% EtOAc in hexane) to give **199** as a clear, colourless oil (49 mg, 90%). R_f (20% EtOAc in hexane) = 0.61; $[\alpha]_D^{23} = -13.4^\circ$ (*c*, 0.51, CHCl₃); $^1\text{H NMR}$ δ (250 MHz, CDCl₃) 7.39-7.04 (8H, m, Ar), 6.84 (2H, s, Ar), 6.79-6.75 (2H, m, Ar), 5.66 (1H, d, $J = 6.1$ Hz, C(1')*HO*), 4.85 (1H, d, $J = 16.3$ Hz, CH_AH_BPh), 4.42 (1H, d, $J = 16.3$ Hz, CH_AH_BPh), 4.04 (1H, qd, $J = 6.8$ & 6.1 Hz, C(2')*H*), 3.66 (1H, dd, $J = 5.9$ & 5.2 Hz, C(3)*H*), 2.55 (1H, qd, $J = 7.2$ & 5.9 Hz, C(2)*H*), 2.39 (6H, s, 2 x CH₃Ar), 2.29 (1H, d, $J = 6.2$ Hz, OH), 2.29 (3H, s, CH₃Ar), 1.72-1.60 (1H, m, C(4)*H*), 1.19 (3H, d, $J = 6.9$ Hz, C(2')H(CH₃), 0.98 (3H, d, $J = 7.2$ Hz, C(2)H(CH₃), 0.93 (9H, t, $J = 8.0$ Hz, 3 x SiCH₂CH₃), 0.83 (3H, d, $J = 6.9$ Hz, C(4)H(CH₃)_Y(CH₃)_Z), 0.76 (3H, d, $J = 6.6$ Hz, C(4)H(CH₃)_Y(CH₃)_Z), 0.58 (6H, q, $J = 8.0$ Hz, 3 x SiCH₂CH₃); $^{13}\text{C NMR}$ δ (62.9 MHz, CDCl₃) 172.9 (C), 142.3 (2C), 138.4 (C), 138.0 (C), 132.9 (C), 132.0 (2CH), 128.2 (2CH), 128.1 (2CH), 128.0 (2CH), 127.7 (2CH), 127.2 (CH), 126.5 (2CH), 78.2 (CH), 77.6 (CH), 56.5 (CH), 48.0 (CH₂), 45.0 (CH), 30.8 (CH), 22.7 (2CH₃), 20.8 (CH₃), 19.6 (CH₃), 17.4 (CH₃), 14.8 (CH₃), 12.7 (CH₃), 6.8 (3CH₃), 5.2 (3CH₂).

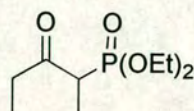
**2'-(*N*-Benzyl-*N*-mesitylenesulfonylamino)-1'-phenylpropyl
(1'*S*,2*S*,2'*R*,3*S*,6*S*,7*R*)-7,9-di-*t*-butyldimethylsilyloxy-2,6-dimethyl-3-
triethylsilyloxynonanoate **200****



To a solution of **197** (478 mg, 0.551 mmol) in CH₂Cl₂ (15 ml) at 0 °C was added dropwise 2,6-lutidine (119 µl, 1.02 mmol) followed after 5 minutes by TES triflate (173 µl, 0.765 mmol) dropwise and the reaction mixture was stirred at 0 °C for 30 min. The reaction mixture was diluted with CH₂Cl₂ (30 ml), washed with NaHCO₃ (50 ml; sat.), NaCl (50 ml; sat.), dried (MgSO₄) and the volatiles removed under reduced pressure. Flash chromatography (CH₂Cl₂) afforded **200** as a clear, colourless oil (513 mg, 95%). *R_f* (CH₂Cl₂) = 0.76; [*α*]_D²³ = -18.2° (*c*, 0.46, CHCl₃); *ν*_{max} (neat)/cm⁻¹ 1741 (C=O); **Major** diastereomer: ¹H NMR δ (600 MHz, CDCl₃) 7.37-7.11 (8H, m, Ar), 6.87 (2H, s, Ar), 6.83-6.80 (2H, m, Ar), 5.75 (1H, d, *J* = 5.1 Hz, C(1')HO), 4.81 (1H, d, *J* = 16.8 Hz, CH_AH_BPh), 4.49 (1H, d, *J* = 16.8 Hz, CH_AH_BPh), 4.07 (1H, qd, *J* = 6.9 & 5.1 Hz C(2')H), 3.95-3.89 (1H, m, C(3)HOTES), 3.69-3.62 (2H, m, C(7)HOTBS and C(9)H_YH_ZOTBS), 3.63-3.57 (1H, m, C(9)H_YH_ZOTBS), 2.57 (1H, dq=qn, *J* = 7.3 Hz, C(2)H), 2.46 (6H, s, 2 x CH₃Ar), 2.30 (3H, s, CH₃Ar), 1.62-1.49 (4H, m, C(6)HCH₃, C(5)H₂ & C(4)H_CH_D), 1.50-1.38 (1H, m, C(4)H_CH_D), 1.36-1.31 (1H, m, C(8)H_WH_X), 1.25-1.19 (1H, m, C(8)H_WH_X), 1.17 (3H, d, *J* = 6.9 Hz, C(2')H(CH₃), 1.02 (3H, d, *J* = 7.3 Hz, C(2)H(CH₃), 0.93 (9H, t, *J* = 8.0 Hz, 3 x SiCH₂CH₃), 0.89 (9H, s, *t*-BuSi), 0.88 (9H, s, *t*-BuSi), 0.79 (3H, d, *J* = 6.6 Hz, C(6)HCH₃), 0.58 (6H, q, *J* = 8.1 Hz, 3 x SiCH₂CH₃), 0.04 (3H, s, SiMe), 0.03 (3H, s, SiMe), 0.02 (3H, s, SiMe), 0.00 (3H, s, SiMe); ¹³C NMR δ (62.9 MHz, CDCl₃) 172.6 (C), 142.3 (C), 140.2 (2 x C), 138.4 (C), 138.2 (C), 133.3 (C), 132.0 (2 x CH), 128.3 (2 x CH), 128.1 (2 x CH), 127.8 (2 x CH), 127.1 (2 x CH), 126.2 (2 x CH), 77.8 (CH), 73.2 (CH), 72.6 (CH), 60.3 (CH₂), 56.6 (CH), 48.1

(CH₂), 45.5 (CH), 39.0 (CH), 34.8 (CH₂), 31.3 (CH₂), 27.6 (CH₂), 25.8 (3 x CH₃), 25.7 (3 x CH₃), 22.7 (2 x CH₃), 20.8 (CH₃), 18.1 (C), 18.0 (C), 13.9 (CH₃), 13.9 (CH₃), 13.6 (CH₃), 11.5 (CH₃), 6.9 (2 x CH₃), 4.9 (3 x CH₃), -4.5 (CH₃), -4.8 (CH₃), -5.4 (2 x CH₃); **HRMS** (FAB, NOBA) [M+H]⁺ found 982.5929, C₅₄H₉₂NO₇SSi₃ requires 982.5902; **m/z** 982 ([M+H]⁺ 1), 686 (1), 406 (59), 223 (39), 134 (78), 77 (69%).

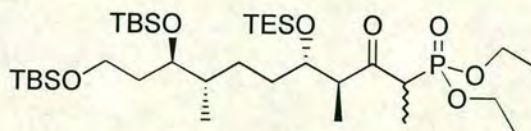
2-Diethoxyphosphorylpentan-3-one 96



General Procedure E was followed with diethyl ethanephosphonate (208 mg, 1.25 mmol) and ⁿBuLi (856 μl, 1.25 mmol, 1.46 M solution in hexanes) in THF (4 ml) which was added to ester **191** (100 mg, 0.209 mmol) in THF (3 ml). Flash chromatography (EtOAc) afforded the free auxiliary **194** (75 mg, 88%) and the phosphonate **96** as a clear, colourless oil (32 mg, 69%). **R_f** (EtOAc) = 0.60.

¹H NMR spectroscopic data identical with that of the compound resulting from the displacement of thioester **88**.

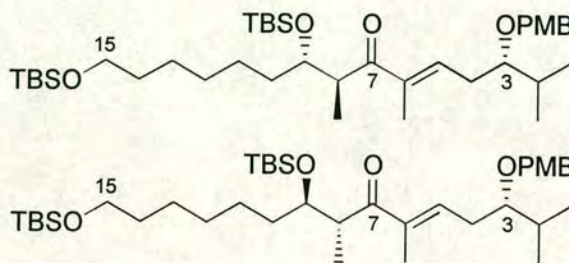
(4*S*,5*S*,8*S*,9*R*)-9,11-Di-*t*-butyldimethylsilyloxy-2-diethoxyphosphoryl-4,8-dimethyl-5-triethylsilyloxy-undecan-3-one **201**



To a solution of diethyl ethanephosphonate (498 mg, 2.98 mmol) in THF (10 ml) was added ⁿBuLi (2.22 ml, 2.98 mmol, 1.35 M solution in hexanes) at -78 °C dropwise and stirred for 45 min at that temperature. The yellow solution was added *via* cannula to a solution of ester **200** (490 mg, 0.209 mmol) in THF (10 ml) and the reaction stirred for a further 15 min followed by 10 min at 0 °C. The orange solution was carefully poured onto NH₄Cl (50 ml; sat.) and extracted with CH₂Cl₂ (3 x 50 ml). The combined organic extracts were washed with NaCl (100 ml, sat.), dried (MgSO₄) and the volatiles removed under reduced pressure. Purification of the crude material by careful flash chromatography (2 columns: 20% EtOAc in hexane followed by 15% EtOAc in hexane) allowed the isolation of the auxiliary (198 mg, 94%), β-ketophosphonate **201** as a clear, colourless oil (*c.* 3:1 mix of diastereomers; 215 mg, 59%) and a small amount of **201** mixed with a minor impurity as a clear, colourless oil (38 mg, 10%). **Major product**: *R*_f (15% EtOAc in hexane) = 0.52; *ν*_{max} (neat)/cm⁻¹ 1716 (C=O); ¹H NMR δ (600 MHz, CDCl₃) 4.13-4.06 (4H, m, P(OCH₂CH₃)₂), 3.97-3.93 (0.25H, m, CHOTES), 3.87-3.83 (0.75H, m, CHOTES), 3.70-3.64 (2H, m, C(9)HOTBS and C(11)*H*_A*H*_BOTBS), 3.63-3.57 (1H, m, C(11)*H*_A*H*_BOTBS), 3.38 (0.75H, dq, *J* = 26.0 & 7.0 Hz, C(2)HP(O)), 3.25 (0.25 H, dq, *J* = 23.5 & 7.0 Hz, C(2)HP(O)), 3.19 (0.75H, dq, *J* = 8.6 & 7.0 Hz, C(4)HC(O)), 2.91 (0.25H, dq=qn, *J* = 7.0 Hz, C(4)HC(O)), 1.64-1.22 (16H, m, C(8)HCH₃, 3 x CH₂, P(OCH₂CH₃)₂ and C(2)HCH₃), 1.08 (0.75H, d, *J* = 7.0 Hz, C(4)HCH₃), 0.96 (2.25H, d, *J* = 7.0 Hz, C(4)HCH₃), 0.92 (2.25H, t, *J* = 8.0 Hz, 3 x SiCH₂CH₃), 0.91 (6.75H, t, *J* = 8.0 Hz, 3 x SiCH₂CH₃), 0.88 (6.75H, s, *t*-BuSi), 0.875 (2.25H, s, *t*-BuSi), 0.87 (6.75 H, s, *t*-BuSi), 0.86 (2.25 H, s, *t*-BuSi), 0.82 (3H, d, *J* = 6.7 Hz, C(8)HCH₃), 0.57 (4.5H, q, *J* = 8.0 Hz, 3 x SiCH₂CH₃), 0.53 (1.5H, q, *J* = 8.0 Hz, 3 x SiCH₂CH₃), 0.03 (4.5H, s, SiMe), 0.026 (1.5H, s, SiMe), 0.023 (2.25H, s, SiMe),

0.02 (0.75H, s, SiMe), 0.015 (2.25H, SiMe), 0.00 (0.75H, SiMe); HRMS (FAB, NOBA) $[M+H]^+$ found 725.4794, $C_{35}H_{78}O_7Si_3P$ requires 725.4793; m/z 725 ($[M+H]^+$ 3), 695 (4), 667 (6), 307 (12), 73 (100%).

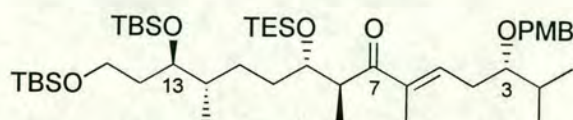
(3*S*,5*E*,8*S*,9*S*)-9,15-Di-*t*-butyldimethylsilyloxy-3-*p*-methoxybenzyloxy-2,6,8-trimethylpentadec-5-en-7-one 202 and **(3*S*,5*E*,8*R*,9*R*)-9,15-Di-*t*-butyldimethylsilyloxy-3-*p*-methoxybenzyloxy-2,6,8-trimethylpentadec-5-en-7-one 203**



To a solution of racemic β -ketophosphonate **102** (56 mg, 0.098 mmol) in THF (1 ml) was added $Ba(OH)_2 \cdot 8H_2O^{\dagger}$ (31 mg, 0.98 mmol) and the mixture stirred for 30 min until it became cloudy. Aldehyde **5** (28 mg, 0.118 mmol) in THF:H₂O (40:1, 1 ml + 1 ml washings) was added and the reaction stirred at room temperature for 24 h, until complete as followed by tlc. The reaction mixture was diluted with CH_2Cl_2 (10 ml), washed with saturated $NaHCO_3$ (10 ml; sat.), $NaCl$ (30 ml; sat.), dried ($MgSO_4$) and the volatiles removed under reduced pressure. Flash chromatography (5% EtOAc in hexane) afforded enones **202** and **203** as a clear, colourless oil (59 mg, 91%). R_f (20% EtOAc in hexane) = 0.62; 1:1 mixture of diastereomers: 1H NMR δ (200 MHz, $CDCl_3$) 7.38-7.31 (2H, m, Ar), 7.00-6.97 (2H, m, Ar), 6.65 (1H, br t, $J = 7.2$ Hz, C(5)*H*), 4.62-4.54 (2H, m, CH_2 Ar), 4.11-4.07 (1H, m, C(9)*H*OTBS), 3.88 (3H, s, $ArOCH_3$), 3.68 (2H, t, $J = 6.5$ Hz, CH_2 OTBS), 3.60-3.37 (2H, m, C(8)*H* and C(3)*H*OPMB), 2.58-2.51 (2H, m, C(4)*H*₂), 2.08-1.89 (1H, m, C(2)*H*), 1.87 (3H, s, C(6)*CH*₃), 1.62-1.28 (10H, m, 5 x CH_2), 1.08-0.88 (27H, m, C(2)*H*(CH_3)₂, C(8)*H*(CH_3), and 2 x *t*-BuSi), 0.13 (6H, s, $SiMe_2$), 0.09 (3H, s, SiMe), 0.00 (3H, s, SiMe).

[†] The Barium Hydroxide was activated by heating in an oven at 120 °C for 2-12 h.

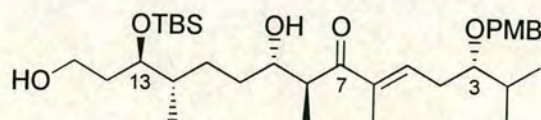
(3*S*,5*E*,8*S*,9*S*,12*S*,13*R*)-13,15-Di-*t*-butyldimethylsilyloxy-3-*p*-methoxybenzyloxy-2,6,8,12-tetramethyl-9-triethylsilyloxy pentadec-5-en-7-one **204**



To a solution of β -ketophosphonate **201** (181 mg, 0.253 mmol) in THF (3 ml) was added $\text{Ba}(\text{OH})_2 \cdot 8\text{H}_2\text{O}$ (80 mg, 0.98 mmol) and the mixture stirred for 40 min until it became cloudy. Aldehyde **5** (72 mg, 0.304 mmol) in THF:H₂O (40:1, 1 ml + 1 ml washings) was added and the reaction stirred at room temperature for 17 h, until complete as followed by tlc. The reaction mixture was diluted with CH_2Cl_2 (40 ml), washed with saturated NaHCO_3 (30 ml; sat.), NaCl (30 ml; sat.), dried (MgSO_4) and the volatiles removed under reduced pressure. Flash chromatography (30% EtOAc in hexane) afforded enone **204** as a clear, colourless oil (170 mg, 83%). R_f (20% EtOAc in hexane) = 0.70; $[\alpha]_D^{23} = +25.4^\circ$ (c 0.35, CHCl_3); ν_{max} (neat)/ cm^{-1} 1666 (C=O); ^1H NMR δ (600 MHz, CDCl_3) 7.26-7.21 (2H, m, Ar), 6.86-6.83 (2H, m, Ar), 6.72 (1H, t, $J = 7.2$ Hz, C(5)*H*), 4.47 (1H, d, $J = 11.2$ Hz, $\text{CH}_A\text{CH}_B\text{Ar}$), 4.44 (1H, d, $J = 11.2$ Hz, $\text{CH}_A\text{CH}_B\text{Ar}$), 4.12-3.97 (1H, m, C(9)*H*OTES), 3.78 (3H, s, ArOCH_3), 3.72-3.65 (2H, m, C(13)*H*OTBS and C(15)*H*_C*H*_DOTBS), 3.63-3.57 (1H, m, C(15)*H*_C*H*_DOTBS), 3.37 (1H, dq, $J = 8.0$ & 7.0 Hz, C(8)*H*), 3.34-3.29 (1H, m, C(3)*H*OPMB), 2.51-2.45 (1H, m, C(4)*H*_E*H*_F), 2.45-2.38 (1H, m, C(4)*H*_E*H*_F), 1.92-1.83 (1H, m, C(2)*H*), 1.78 (3H, d, $J = 0.7$ Hz, C(6)*CH*₃), 1.63-1.46 (4H, m, C(12)*HCH*₃, C(11)*H*₂ & C(10)*H*_G*H*_HCHOTES), 1.44-1.32 (2H, m, C(10)*H*_G*H*_HCHOTES & C(14)*H*_J*H*_KCH₂OTBS), 1.15-1.06 (1H, m, C(14)*H*_J*H*_KCH₂OTBS), 0.95 (3H, d, $J = 7.0$ Hz, C(8)*H*(*CH*₃), 0.92 (3H, d, $J = 6.8$ Hz, C(2)*H*(*CH*₃)_A), 0.91 (3H, d, $J = 6.9$ Hz, C(2)*H*(*CH*₃)_B), 0.88 (9H, s, *t*-BuSi), 0.87 (9H, t, $J = 8.0$ Hz, 3 x SiCH_2CH_3), 0.87 (9H, s, *t*-BuSi), 0.85 (3H, d, $J = 6.8$ Hz, C(12)*HCH*₃), 0.50 (6H, q, $J = 8.0$ Hz, 3 x SiCH_2CH_3), 0.03 (6H, s, 2 x SiMe), 0.025 (3H, s, SiMe), 0.017 (3H, s, SiMe); ^1H NMR decoupling experiments δ (600 MHz, CDCl_3) Irradiation at 4.05 led to simplification at 3.37, 1.63-1.46 and 1.44-1.32, irradiation at 3.37 led to

simplification at 4.12-3.97 and 0.95 and irradiation at 2.45 caused simplification at 3.34-3.29 and 6.72; ^{13}C NMR δ (50.3 MHz, CDCl_3) 204.8, 159.0, 139.4, 138.2, 130.7, 129.1 (2C), 113.6 (2C), 82.8, 74.1, 72.6, 71.5, 60.4, 55.1, 44.4, 39.4, 34.8, 32.2, 31.1, 30.6, 26.9, 25.8 (7C), 18.1, 18.0, 17.9, 14.0, 13.7, 11.8, 6.8 (3C), 4.9 (3C), -4.6, -4.8, -5.5 (2C); HRMS (FAB, NOBA) $[\text{M}+\text{H}]^+$ found 807.5823, $\text{C}_{45}\text{H}_{87}\text{O}_6\text{Si}_3$ requires 807.5811; m/z 807 ($[\text{M}+\text{H}]^+$ 1), 641 (5), 371 (6), 239 (38), 73 (100%).

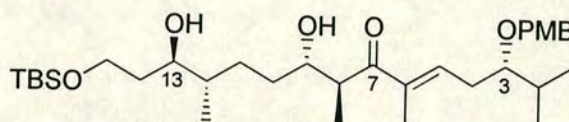
(3*S*,5*E*,8*S*,9*S*,12*S*,13*R*)-13-*t*-Butyldimethylsilyloxy-9,15-dihydroxy-3-*p*-methoxybenzyloxy-2,6,8,12-tetramethylpentadec-5-en-7-one 205



To a stirred solution of **204** (104 mg, 0.129 mmol) in THF (3 ml) and H_2O (0.6 ml) was added TFA (30 μl , 0.387 mmol) and the reaction stirred at room temperature for 6 h. The reaction mixture was quenched by pouring onto NaHCO_3 (5 ml; sat.), extracted with EtOAc (3 x 5 ml), dried (MgSO_4) and the volatiles removed under reduced pressure. Flash chromatography (50% EtOAc in hexane) afforded **207** (8.0 mg, 11%), the triol **206** (≤ 0.1 mg) and diol **205** as a clear, colourless oil (43 mg, 60%). R_f (50% EtOAc in hexane) = 0.56; $[\alpha]_D^{25} = +7.4^\circ$ (c 1.0, CHCl_3); ν_{max} (neat)/ cm^{-1} 3452 (OH), 1658 (C=O); ^1H NMR δ (600 MHz, CDCl_3) 7.29-7.21 (2H, m, Ar), 6.87-6.85 (2H, m, Ar), 6.75-6.71 (1H, m, C(5)*H*), 4.48 (1H, d, $J = 11.2$ Hz, $\text{CH}_\text{A}\text{CH}_\text{B}\text{Ar}$), 4.44 (1H, d, $J = 11.2$ Hz, $\text{CH}_\text{A}\text{CH}_\text{B}\text{Ar}$), 3.79 (3H, s, ArOCH_3), 3.78-3.74 (1H, m, C(13)*H*OTBS), 3.74-3.68 (2H, m, C(15)*H* $_2$ OH), 3.69-3.62 (1H, m, C(9)*H*OH), 3.31 (1H, ddd, $J = 6.2, 6.2$ & 5.7 Hz, C(3)*H*OPMB), 3.21 (1H, dq, $J = 7.4$ & 6.8 Hz, C(8)*H*), 2.96 (1H, br d, $J = 7.0$ Hz, C(9)*H*OH), 2.45 (2H, dd, $J = J' = 6.2$ Hz, C(4)*H* $_2$), 2.08 (1H, br t, $J = 5.1$ Hz C(15)*H* $_2$ OH), 1.94-1.88 (1H, m, C(2)*H*), 1.79 (3H, d, $J = 1.0$ Hz, C(6)*CH* $_3$), 1.68-1.47 (3H, m, C(12)*HCH* $_3$ and C(11)*H* $_2$), 1.44-1.30 (3H, m, C(10)*H* $_2$ CHOH & C(14)*H* $_C$ *H* $_D$ CH $_2$ OH), 1.32-1.24 (1H, m, C(14)*H* $_C$ *H* $_D$ CH $_2$ OH), 1.12 (3H, d, $J = 6.8$ Hz, C(8)*HCH* $_3$), 0.96 (3H, d, $J = 6.7$ Hz, C(2)*H*(*CH* $_3$) $_A$), 0.92 (3H, d, $J = 6.8$ Hz, C(2)*H*(*CH* $_3$) $_B$), 0.88 (9H, s, *t*-BuSi), 0.85

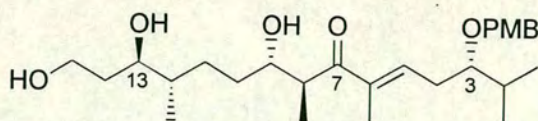
(3H, d, $J = 6.7$ Hz, C(12)HCH₃), 0.06 (3H, s, SiMe), 0.05 (3H, s, SiMe); ¹H NMR decoupling experiments δ (600 MHz, CDCl₃) Irradiation at 3.21 led to simplification at 3.69-3.62 and 1.12, irradiation at 2.08 caused simplification at 3.74-3.68; ¹³C NMR δ (150 MHz, CDCl₃) 207.1, 159.1, 140.9, 137.8, 130.5, 129.2 (2C), 113.7 (2C), 82.5, 74.7, 74.1, 71.3, 60.7, 55.1, 43.9, 38.4, 33.4, 32.9, 31.0, 30.3, 29.1, 25.7 (3C), 18.4, 17.90, 17.88, 16.1, 13.7, 11.4, -4.4, -4.7; HRMS (FAB, NOBA) [M+H]⁺ found 579.4093, C₄₅H₈₇O₆Si₃ requires 579.4081; m/z 579 ([M+H]⁺ 1), 289 (2), 189 (5), 154 (12), 121 (100%).

(3*S*,5*E*,8*S*,9*S*,12*S*,13*R*)-15-*t*-Butyldimethylsilyloxy-9,13-dihydroxy-3-*p*-methoxybenzyloxy-2,6,8,12-tetramethyl pentadec-5-en-7-one 207



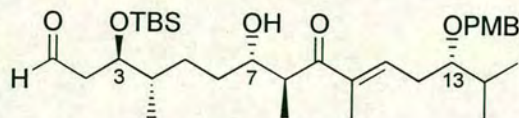
R_f (50% EtOAc in hexane) = 0.76; ¹H NMR δ (200 MHz, CDCl₃) 7.24-7.18 (2H, m, Ar), 6.84-6.78 (2H, m, Ar), 6.70 (1H, br t, $J = 6.4$ Hz, C(5)H), 4.49-4.38 (2H, m, CH₂Ar), 3.78 (3H, s, ArOCH₃), 3.74-3.51 (4H, m, CH₂OTBS, C(9)HOH and C(13)HOH), 3.28 (1H, dt, $J = 6.1$ & 5.9 Hz, C(3)HOPMB), 3.25-3.18 (1H, m, C(8)H), 2.84 (1H, br d, $J = 7.0$ Hz, CHOH), 2.43 (2H, dd, $J = J' = 6.1$ Hz, C(4)H₂), 1.94-1.82 (1H, m, C(2)H), 1.77 (3H, br s, C(6)CH₃), 1.61-1.14 (7H, m, C(12)HCH₃, C(11)H₂CH₂CHOH, C(10)H₂CHOH and C(14)H₂CH₂OH), 1.09 (3H, d, $J = 6.9$ Hz, C(8)H(CH₃), 0.93 (3H, d, $J = 7.0$ Hz, C(2)H(CH₃)_A), 0.90 (3H, d, $J = 7.0$ Hz, C(2)H(CH₃)_B), 0.85 (9H, s, *t*-BuSi), 0.84 (3H, d, $J = 6.9$ Hz, C(12)HCH₃), 0.00 (6H, s, 2 x SiMe).

(3*S*,5*E*,8*S*,9*S*,12*S*,13*R*)-3-*p*-Methoxybenzyloxy-2,6,8,12-tetramethyl-9,13,15-trihydroxy pentadec-5-en-7-one 206



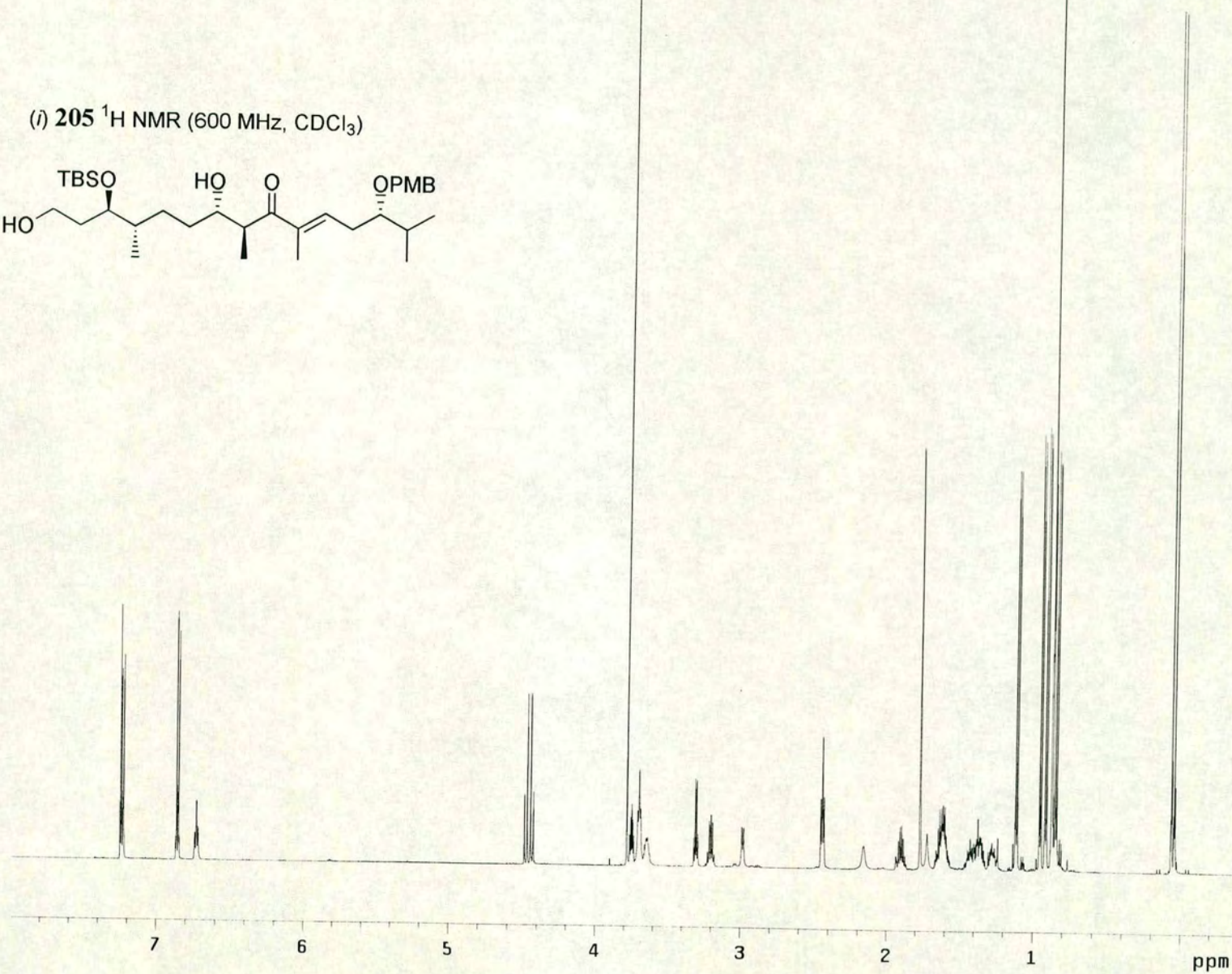
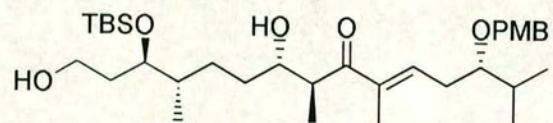
R_f (EtOAc) = 0.42; ^1H NMR δ (600 MHz, CDCl_3) 7.26-7.23 (2H, m, Ar), 6.88-6.85 (2H, m, Ar), 6.75-6.71 (1H, td, $J = 7.0$ & 0.9 Hz, C(5) H), 4.48 (1H, d, $J = 11.3$ Hz, $\text{CH}_\text{A}\text{CH}_\text{B}\text{Ar}$), 4.43 (1H, d, $J = 11.3$ Hz, $\text{CH}_\text{A}\text{CH}_\text{B}\text{Ar}$), 3.89-3.83 (1H, m, C(15) $H_\text{A}H_\text{B}\text{OH}$), 3.84-3.78 (1H, m, C(15) $H_\text{A}H_\text{B}\text{OH}$), 3.79 (3H, s, ArOCH_3), 3.72-3.61 (2H, m, C(13) HOH and C(9) HOH), 3.31 (1H, ddd, $J = 6.3, 6.3$ & 5.7 Hz, C(3) HOPMB), 3.21 (1H, qd, $J = 7.1$ & 6.8 Hz, C(8) H), 3.12 (1H, br d, $J = 6.8$ Hz, CHOH), 2.72 (1H, br s, OH), 2.58 (1H, br s, OH), 2.43 (2H, dd, $J = 7.0$ & 6.3 Hz, C(4) H_2), 1.94-1.87 (1H, m, C(2) H), 1.78 (3H, d, $J = 0.9$ Hz, C(6) CH_3), 1.72-1.60 (3H, m, C(12) HCH_3 and C(11) $\text{H}_2\text{CH}_2\text{CHOH}$), 1.58-1.32 (4H, m, C(10) H_2CHOH & C(14) $\text{H}_2\text{CH}_2\text{OH}$), 1.15 (3H, d, $J = 7.1$ Hz, C(8) HCH_3), 0.96 (3H, d, $J = 6.8$ Hz, C(2) $\text{H}(\text{CH}_3)_\text{A}$), 0.92 (3H, d, $J = 6.8$ Hz, C(2) $\text{H}(\text{CH}_3)_\text{B}$), 0.86 (3H, d, $J = 7.0$ Hz, C(12) HCH_3).

(3*R*,4*S*,7*S*,8*S*,10*E*,13*S*)-3-*t*-Butyldimethylsilyloxy-7-hydroxy-13-*p*-methoxybenzyloxy-9-oxo-4,8,10,14-tetramethyl-pentadec-10-enal **208**

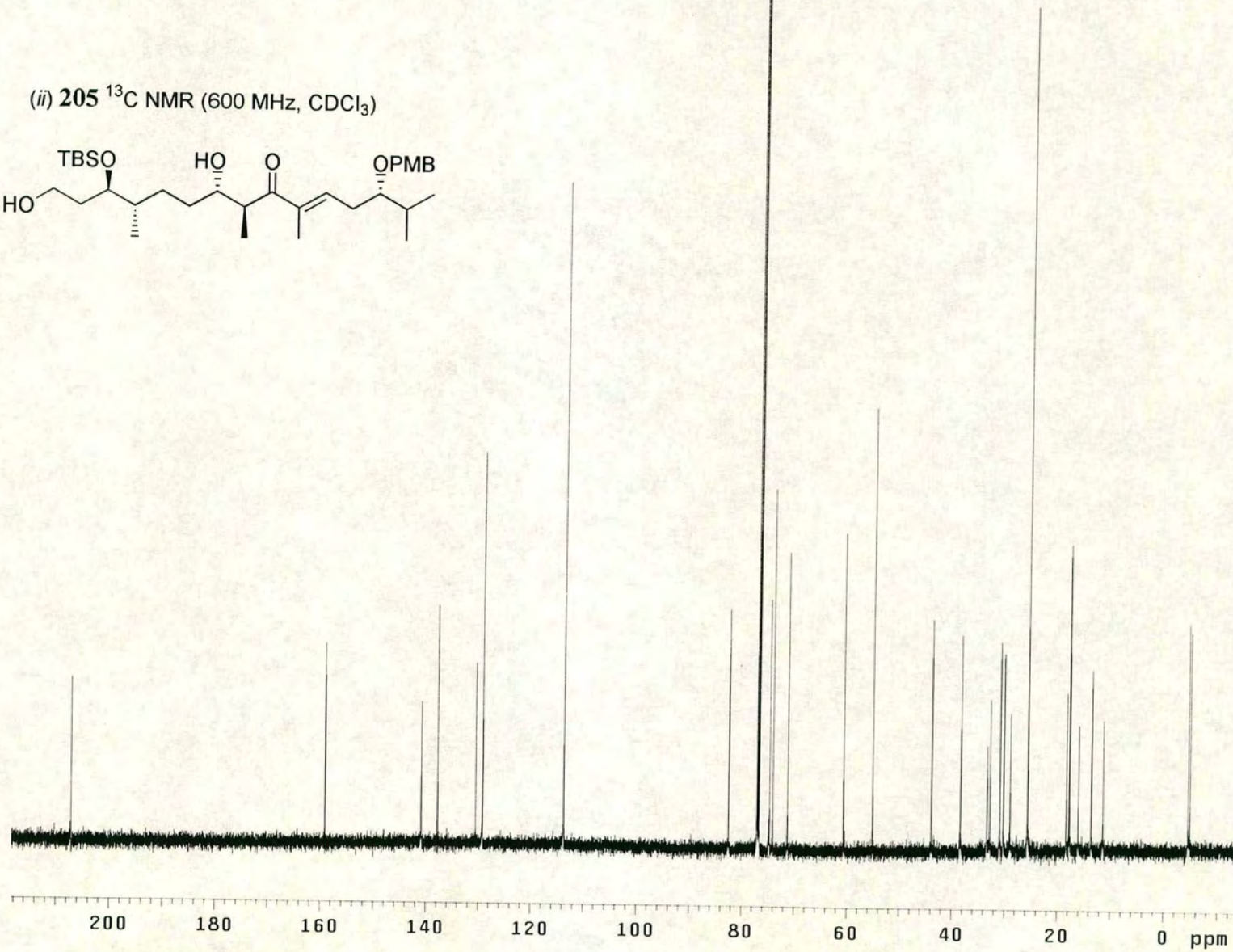
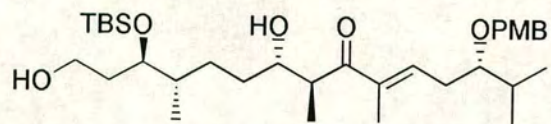


General procedure H was followed with diol **205** (30.0 mg, 0.052 mmol), TEMPO (0.2 mg, 1.04 μ mol), tetra-*n*-butylammonium chloride (0.7 mg, 2.06 μ mol), sodium bromide (0.5 mg, 5.20 μ mol), CH_2Cl_2 (1 ml) and NaHCO_3 (1 ml; sat.) to which was added NaOCl (64 μ l of a 1.06 M aqueous solution, 0.067 mmol) in NaHCO_3 (0.1 ml; sat.) and NaCl (0.2 ml; sat.). The residual orange oil was passed quickly through a short plug of silica (40% EtOAc in hexane) to remove the residual starting material to give a clear, unstable oil **208** (14.2 mg, 47%) which was used without further purification in the next step. R_f (50% EtOAc in hexane) = 0.86; ν_{max} (neat)/ cm^{-1} 3444 (OH), 1721 (C=O aldehyde), 1652 (C=O ketone); ^1H NMR δ (200 MHz, CDCl_3) 9.76 (1H, t, J = 2.8 Hz, HC=O), 7.24-7.20 (2H, m, Ar), 6.86-6.82 (2H, m, Ar), 6.72 (1H, br t, J = 7.0 Hz, C(11)*H*), 4.48 (1H, d, J = 11.2 Hz, $\text{CH}_\text{A}\text{CH}_\text{B}\text{Ar}$), 4.40 (1H, d, J = 11.2 Hz, $\text{CH}_\text{A}\text{CH}_\text{B}\text{Ar}$), 4.12-4.02 (1H, m, C(3)*H*OTBS), 3.77 (3H, s, ArOCH_3), 3.70-3.54 (1H, m, C(7)*H*OH), 3.46-3.21 (1H, m, C(13)*H*OPMB), 3.24-3.11 (1H, m, C(8)*H*), 2.94 (1H, br d, J = 3.8 Hz, C(7)*H*OH), 2.57-2.46 (4H, m, C(2)*HC=O* and C(12)*H*₂), 1.95-1.82 (1H, m, C(14)*H*), 1.76 (3H, br s, C(10)*CH*₃), 1.70-1.15 (5H, m, C(4)*HCH*₃, C(5)*H*₂ and C(6)*H*₂CHOH), 1.11 (3H, d, J = 7.0 Hz, C(8)*HCH*₃), 0.93 (3H, d, J = 7.0 Hz, C(2)*H*(*CH*₃)_A), 0.90 (3H, d, J = 7.2 Hz, C(2)*H*(*CH*₃)_B), 0.85 (3H, d, J = 6.8 Hz, C(4)*HCH*₃), 0.83 (9H, s, *t*-BuSi), 0.03 (3H, s, SiMe), 0.00 (3H, s, SiMe).

(i) **205** ^1H NMR (600 MHz, CDCl_3)



(ii) **205** ^{13}C NMR (600 MHz, CDCl_3)



REFERENCES

- (1) Rousseau, G. *Tetrahedron* **1995**, 51, 2777.
- (2) Fang, X.-p.; Anderson, J. E.; Qiu, X.-x.; Kozlowski, J. F.; Chang, C.-j.; McLaughlin, J. L. *Tetrahedron* **1993**, 49, 1563.
- (3) Kinjo, J. *Tetrahedron Lett.* **1985**, 26, 6101.
- (4) Tamelan, E. E. V.; Dickie, J. P.; Loomans, M. E.; Dewey, R. S.; Strong, R. S. *J. Am. Chem. Soc.* **1961**, 83, 1639.
- (5) Lindquist, N.; Fenical, W. *Tetrahedron Lett.* **1989**, 30, 2735.
- (6) Aimi, N.; Uchida, N.; Ohya, N.; Hosokawa, H.; Takayama, H.; Sakai, S.-i.; Mendoza, L. A.; Polz, L.; Stöckigt, J. *Tetrahedron Lett.* **1991**, 32, 4949.
- (7) Tapiolas, D. M.; Roman, M.; Fenical, W.; Stout, T. J.; Clardy, J. *J. Am. Chem. Soc.* **1991**, 113, 4682.
- (8) Fenical, W. *Chem Rev* **1993**, 1680.
- (9) Kupchan, S. M.; Schubert, R. M. *Science* **1974**, 185, 791.
- (10) Lillehaug, J. R.; Kleppe, K.; Kupchan, S. M. *Biochim. Biophys. Acta* **1973**, 92, 327.
- (11) Tannock, I. F.; Hill, R. P. *The Pharmacology of Anti Cancer Drugs*; Pergamon Press: New York, 1987.
- (12) Fenical, W., Personal Communication.
- (13) Perchellet, J. P.; Perchellet, E. M.; Newell, S. W.; Freeman, J. A.; Ladesich, J. B.; Jeong, Y.; Sato, N.; Buszek, K. *Anticancer Res.* **1998**, 18, 97.
- (14) Norcross, R. D.; Paterson, I. *Chem. Rev.* **1995**, 95, 2041.
- (15) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, 79, 1920.
- (16) Brown, H. C.; Ganesan, K.; Dhar, R. K. *J. Org. Chem.* **1993**, 58, 147.
- (17) Gennari, C.; Hewkin, C. T.; Molinari, F.; Bernardi, A.; Comotti, A.; Goodman, J. M.; Paterson, I. *J. Org. Chem.* **1992**, 57, 5173.
- (18) Gennari, C.; Moresca, D.; Vieth, S.; Vulpetti, A. *Angew. Chem. Int. Ed. Engl.* **1993**, 32, 1618.
- (19) Goodman, J. M. *Tetrahedron Lett.* **1992**, 47, 7219.
- (20) Goodman, J. M.; Paterson, I. *Tetrahedron Lett.* **1992**, 33, 7223.

- (21) Corey, E. J. *J. Am. Chem. Soc.* **1990**, *112*, 4976.
- (22) Cowden, C. J.; Paterson, I. *Org. React.* **1997**, *51*, 1.
- (23) Duthaler, R. O.; Herold, P.; Wyler-Helfer, S.; Riediker, M. *Helv. Chim. Acta* **1990**, *73*, 659.
- (24) Narasaka, K.; Miwa, T. *Chem. Lett.* **1985**, 1217.
- (25) Oppolzer, W.; Lienard, P. *Tetrahedron Lett.* **1993**, *34*, 4321.
- (26) Paterson, I.; Wallace, D. J.; Velazquez, S. M. *Tetrahedron Lett.* **1994**, *35*, 9083.
- (27) Abiko, A.; Liu, J.-F.; Masamune, S. *J. Am. Chem. Soc.* **1997**, *119*, 2586.
- (28) Yoshimitsu, T.; Song, J. J.; Wang, G.-Q.; Masamune, S. *J. Org. Chem.* **1997**, *62*, 8978.
- (29) Bernardi, A.; Cassinari, A.; Comotti, A.; Gardner, M.; Gennari, C.; Goodman, J. M.; Paterson, I. *Tetrahedron* **1992**, *48*, 4183.
- (30) Denmark, S. E.; Stavenger, R. A.; Wong, K.-T. *J. Org. Chem.* **1998**, *63*, 918.
- (31) Singer, R. A.; Carreira, E. M. *Tetrahedron Lett.* **1997**, *38*, 927.
- (32) Evans, D. A.; Sjogren, E. B.; Weber, A. W.; Conn, R. E. *Tetrahedron Lett.* **1987**, *28*, 39.
- (33) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127.
- (34) Davies, S. G.; Dordor, I. M.; Warner, P. *J. Chem. Soc., Chem. Commun.* **1984**, 956.
- (35) Yan, T.-H.; Hung, A.-W.; Lee, H.-C.; Chang, C.-S.; Liu, W.-H. *J. Org. Chem.* **1995**, *60*, 3301.
- (36) Fürstner, A. *Synthesis* **1989**, 571.
- (37) Fukuzawa, S.-i.; Tatsuzawa, M.; Hirano, K. *Tetrahedron Lett.* **1998**, *39*, 6899.
- (38) Kagoshima, H.; Hashimoto, Y.; Oguru, D.; Saigo, K. *J. Org. Chem.* **1998**, *63*.
- (39) Wessjohann, L.; Gabriel, T. *J. Org. Chem.* **1997**, *62*, 3772.
- (40) Gabriel, T.; Wessjohann, L. *Tetrahedron Lett.* **1997**, *38*, 4387.
- (41) Breuer, E.; Zbaida, S.; Segall, E. **1979**, 2203.
- (42) Durrant, G.; Sutherland, J. K. *J. Chem. Soc., Perkin Trans I* **1972**, 2582.
- (43) Sturtz, G. *Bull. Soc. Chim. Fr.* **1964**.

- (44) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, 24, 4405.
- (45) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfield, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, 25, 2183.
- (46) Paterson, I.; Yeung, K.-S.; Smaill, J. B. *Synlett* **1993**, 774.
- (47) Sinisterra, J. V.; Marinas, J. M.; Riquelme, F.; Arias, M. S. *Tetrahedron* **1988**, 44, 1431.
- (48) Jantsch, G.; Skalla, N. Z. *Anorg. Chem.* **1930**, 193, 391.
- (49) Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, 102, 2693.
- (50) Molander, G.; Harris, C. R. *Chem. Rev.* **1996**, 96, 307.
- (51) Molander, G. *Org. React.* **1994**, 46, 211.
- (52) Namy, J. L.; Girard, P.; Kagan, H. B.; Caro, P. E. *Nouv. J. Chim.* **1980**, 5, 479.
- (53) Imamoto, T.; Ono, M. *Chem. Lett.* **1987**, 501.
- (54) Deacon, G. B.; Forsyth, C. M. *Chem. Lett.* **1989**, 837.
- (55) Johnson, D. A. *J. Chem. Soc., Dalton* **1974**, 1671.
- (56) Shabangi, M.; Flowers, R. A. *Tetrahedron Lett.* **1997**, 38, 1137.
- (57) Soderquist, J. A. *Aldrichimica Acta* **1991**, 24, 15.
- (58) Namy, J. L.; Souppe, J.; Collin, J.; Kagan, H. B. *J. Org. Chem.* **1984**, 49, 2045.
- (59) Uenishi, J.; Masuda, S.; Wakabayashi, S. *Tetrahedron Lett.* **1991**, 32, 5097.
- (60) Onozawa, S.; Sakakura, T.; Tanaka, M.; Shiro, M. *Tetrahedron* **1996**, 52, 4291.
- (61) Lange, G. L.; Organ, M. G. *Synlett* **1991**, 665.
- (62) Umekawa, Y.; Sakaguchi, S.; Nishiyama, Y.; Ishii, Y. *J. Org. Chem.* **1997**, 62, 3409.
- (63) Evans, D. A.; Hoveyda, A. H. *Journal of the American Chemical Society* **1990**, 112, 6447.
- (64) Romo, D.; Meyer, S. D.; Johnson, D. D.; Schrieber, S. L. *Journal of the American Chemical Society* **1993**, 115, 7906.
- (65) Paterson, I.; Woodrow, M. D.; Cowden, C. J. *Tetrahedron Lett.* **1998**, 39, 6041.

- (66) Andrus, M. B.; Argade, A. B. *Tetrahedron Lett.* **1996**, 37, 5049.
- (67) Bach, J.; Berenguer, R.; Garcia, J.; Villarrasa, J. *Tetrahedron Lett.* **1995**, 36, 3425.
- (68) Buszek, K. R.; Sato, N.; Jeong, Y. *Journal of the American Chemical Society* **1994**, 116, 5511.
- (69) Hulme, A. N.; Howells, G. E. *Tetrahedron Lett.* **1997**, 38, 8245.
- (70) Kodama, M.; Matsushita, M.; Terada, Y.; Takeuchi, A.; Yoshio, S.; Fukuyama, Y. *Chem. Lett.* **1997**, 117.
- (71) Inoue, S.; Iwabuchi, Y.; Irie, H.; Hatakeyama, S. *Synlett* **1998**, 735.
- (72) McWilliams, J. C.; Clardy, J. *J. Am. Chem. Soc.* **1994**, 116, 8378.
- (73) Nagao, Y.; Hagiwara, Y.; Kumagai, T.; Ochiai, M.; Inoue, T. *J. Org. Chem.* **1986**, 51, 2391.
- (74) McDougal, P. G. *J. Org. Chem.* **1986**, 51, 3388.
- (75) Kalinowski, H. O.; Crass, G.; Seebach, D. *Chem. Ber* **1981**, 114, 477.
- (76) Pattison, F. L.; Stothers, J. B.; Woolford, R. G. *J. Am. Chem. Soc.* **1956**, 78, 2255.
- (77) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, 113, 7277.
- (78) Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, 35, 8019.
- (79) Corey, E. J.; Palani, A. *Tetrahedron Lett.* **1995**, 36, 3485.
- (80) Terauchi, T.; Nakata, M. *Tetrahedron Lett.* **1998**, 39, 3795.
- (81) Gennari, C.; Beretta, M. G.; Bernadi, A.; Moro, G.; Scolastico, C.; Todeschini, R. *Tetrahedron* **1986**, 42, 893.
- (82) Masamune, S.; Sato, S.; Kim, B. M.; Wollmann, T. A. *J. Am. Chem. Soc.* **1986**, 108, 8279.
- (83) Paterson, I.; Hulme, A. N. *J. Org. Chem.* **1995**, 60, 3288.
- (84) Masamune, S. *Aldrichimica Acta* **1978**, 11, 23.
- (85) Ley, S. V.; Smith, S. C.; Woodward, P. R. *Tetrahedron* **1992**, 48, 1145.
- (86) Mukaiyama, T. *Aldrichimica Acta* **1996**, 29, 59.
- (87) Delamarche, I.; Mosset, P. *J. Org. Chem.* **1994**, 59, 5453.
- (88) Hulme, A. N.; Howells, G. E.; Walker, R. H. *Synlett* **1998**, 828.
- (89) Maryanoff, B. E.; Reitz, A. B. *Chemical Society Reviews* **1989**, 89, 863.

- (90) Koskinen, A. M. P.; Koskinen, P. M. *Synlett* **1993**, 501.
- (91) Mulzer, J.; Berger, M. *Tetrahedron Lett.* **1998**, 39, 803.
- (92) Stocksdales, M. G.; Ramurthy, S.; Miller, M. J. *J. Org. Chem.* **1998**, 63, 1221.
- (93) Siedlecka, R.; Skarzewski, J.; Mlochowski, J. *Tetrahedron Lett.* **1990**, 31, 2177.
- (94) Paterson, I.; Rawson, D. J. *Tetrahedron Lett.* **1989**, 30, 7463.
- (95) Nooy, A. E. J. d.; Besemer, A. C.; Bekkum, H. v. *Synthesis* **1996**, 1153.
- (96) Leanna, M. R.; Sowin, T. J.; Morton, H. E. *Tetrahedron Lett.* **1992**, 33, 5029.
- (97) Kawatsura, M.; Kishi, E.; Kito, M.; Sakai, T.; Shirahama, H.; Matsuda, F. *Synlett* **1997**, 479.
- (98) Romo, D.; Meyer, S. D.; Johnson, D. D.; Schrieber, S. L. *J. Am. Chem. Soc.* **1993**, 115, 7906.
- (99) Schwaeb, M. K.; Little, R. D. *Syn. Comm.* **1997**, 27, 837.
- (100) Mahrwald, R.; Costisella, B. *Synthesis* **1996**, 1087.
- (101) Kiefel, M. J.; Maddock, J.; Pattenden, G. *Tetrahedron Lett.* **1992**, 33, 3227.
- (102) Finan, J. M.; Kishi, Y. *Tetrahedron Lett.* **1984**, 23, 2719.
- (103) Ohno, K.; Nishiyama, H.; Nagase, H. *Tetrahedron Lett.* **1979**, 4405.
- (104) Yang, H. W.; Zhao, C.; Romo, D. *Tetrahedron* **1997**, 53, 16471.
- (105) Pommier, A.; Pons, J.-M. *Synthesis* **1995**, 729.
- (106) Evans, D. A.; Ratz, A. M.; Huff, B. E.; Sheppard, G. S. *J. Am. Chem. Soc.* **1995**, 117, 3448.
- (107) Banks, M. R.; Cadogan, J. I. G.; Gosney, I.; Grant, K. J.; Hodgson, P. K. G.; Thorburn, P. *Heterocycles* **1994**, 37, 199.
- (108) Braslau, R.; Kuhn, H.; Burrill, L. C.; Lanham, K.; Stenland, C. J. *Tetrahedron Lett.* **1996**, 37, 7933.
- (109) González, Á.; Aiguadé, J.; Urpí, F.; Vilarrasa, J. *Tetrahedron Lett.* **1996**, 37, 8949.
- (110) McKennon, M. J.; Meyers, A. I.; Drauz, K.; Schwarm, M. *J. Org. Chem.* **1993**, 58, 3568.
- (111) Delaunay, D.; Toupet, L.; Corre, M. L. *J. Org. Chem.* **1995**, 60, 6604.

- (112) Nakajima, N.; Horita, K.; Abe, R.; Yonemitsu, O. *Tetrahedron Lett.* **1988**, 29, 4139.
- (113) Kocienski, P. J. *Protecting Groups*; Georg Thieme Verlag: Stuttgart; New York, 1994.
- (114) Takano, S.; Akiyama, M.; Sato, S.; Ogasawara, K. *Chem. Lett.* **1983**, 1593.
- (115) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, 102, 5974.
- (116) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, 109, 5765.
- (117) Avalos, M.; Babiano, R.; Cintas, P.; Jiménez, J. L.; Palacios, J. C. *Tetrahedron Asymm.* **1997**, 8, 2997.
- (118) Taber, D. F.; Houze, J. B. *J. Org. Chem.* **1994**, 59, 4004.
- (119) Sheppeck, J. E.; Liu, W.; Chamberlain, R. *J. Org. Chem.* **1997**, 62, 387.
- (120) Chérest, M.; Felkin, H. *Tetrahedron Lett.* **1968**, 2199.
- (121) Anh, N. T.; Eisenstein, O. *Nouv. J. de Chim.* **1977**, 1, 61.
- (122) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, 95, 512.
- (123) Ohtani, I.; Kusumi, T.; Yashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, 113, 4092.
- (124) Gabriel, T.; Wessjohann, L. *Tetrahedron Lett.* **1997**, 38, 4387.
- (125) Wessjohann, L. Personal Communication.
- (126) Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1987**, 109, 7151.
- (127) Seebach, D.; Chow, H.-F.; Jackson, R. F. W.; Sutter, M. A.; Thaisrivongs, S.; Zimmerman, J. *Liebigs Ann. Chem.* **1986**, 1281.
- (128) Boschelli, D.; Takemasa, T.; Nishitani, Y.; Masamune, S. *Tetrahedron Lett.* **1985**, 26, 5239.
- (129) Jones, T. K.; Reamer, R. A.; Desmond, R.; Mills, S. G. *J. Am. Chem. Soc.* **1990**, 112, 2998.
- (130) Nicolaou, K. C.; Xu, J. Y.; Kim, S.; Pfefferkorn, J.; Ohshima, T.; Vourloumis, D.; Hosokawa, S. *J. Am. Chem. Soc.* **1998**, 120, 8661.
- (131) Evans, D. A.; Nelson, S. G.; Gagne, M. R.; Muci, A. R. *J. Am. Chem. Soc.* **1993**, 115, 9800.

- (132) Perrin, D. A.; Amarego, W. L. F. *Purification of Laboratory Chemicals*; Pergamon Press: Oxford, 1988.
- (133) Casey, M.; Leonard, J.; Lygo, B.; Procter, G. *Advanced Practical Organic Chemistry*; Blackie: London, 1990.
- (134) Marshall, J. A.; Shearer, B. G.; Crooks, S. L. *J. Org. Chem.* **1987**, 52, 1236.
- (135) Nishida, A.; Kawahara, N.; Nishida, M.; Yonemitsu, O. *Tetrahedron* **1996**, 52, 9713.
- (136) Trost, B. M.; Tometzki, G. B. *Synthesis* **1991**, 1235.
- (137) Schleppnik, A. A.; Zienty, F. B. *J. Org. Chem.* **1964**, 29, 1910.
- (138) Hulme, A. N. PhD, Cambridge, **1993**.
- (139) Coutrot, P.; Ghribi, A. *Synthesis* **1986**, 661.
- (140) Bonini, C.; Checconi, M.; Righi, G.; Leucio, R. *Tetrahedron* **1995**, 51, 4111.
- (141) Pattenden, G. Personal Communication.
- (142) *Aldrich Chemical Catalogue* **1997-1998**.
- (143) Buechi, G. *J. Chem. Soc.* **1961**, 2843.
- (144) Vigneron, J. P. *Tetrahedron* **1977**, 33, 507.
- (145) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, 118, 4322.
- (146) Evans, D. A. Personal Communication.

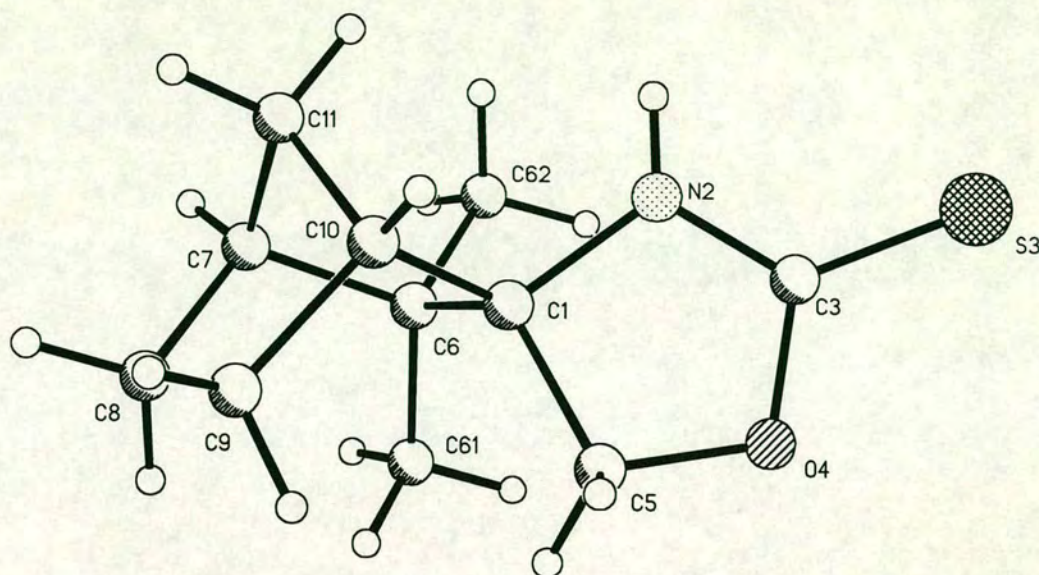


Figure 1 Crystal structure of oxazolidinethione **145**

Table 1 Crystal data and structure refinement for oxazolidinethione **145**

Empirical formula	C ₁₁ H ₁₇ NOS
Formula weight	211.32
Wavelength	1.54184 Å
Temperature	220(2) K
Crystal system	Monoclinic
Space group	P21
Unit cell dimensions	a = 7.7239(8) Å alpha = 90 deg
	b = 14.1846(14) Å beta = 94.246(8) deg
	c = 10.1371(10) Å gamma = 90 deg
Volume	1107.58(19) Å ³
Number of reflections for cell	78 (20 < theta < 22 deg.)
Z	4
Density (calculated)	1.267 Mg/m ³
Absorption coefficient	2.328 mm ⁻¹
F(000)	456

PART A Crystal data

Crystal description	Colourless block
Crystal size	0.50 x 0.43 x 0.39 mm
Theta range for data collection	4.37 to 69.89 deg.
Index ranges	-9<= <i>h</i> <=9, -17<= <i>k</i> <=16, -3<= <i>l</i> <=12
Reflections collected	3643
Independent reflections	2513 [R(int) = 0.0127]
Scan type	Omega-theta
Absorption correction	Numerical (T _{min} = 0.348, T _{max} = 0.471)

PART B Data collection

Solution	Patterson (DIRDIF)
Refinement type	Full-matrix least-squares on F ²
Program used for refinement	SHELXL-97
Hydrogen atom placement	geometric/difference map (CH ₃ ,NH)
Hydrogen atom treatment	Riding/rotating group (CH ₃)/refall(NH)
Data/restraints/parameters	2513/1/267
Goodness-of-fit on F ²	1.063
Conventional R [F>4σ(F)]	R1 = 0.0213 [2487 data]
Weighted R (F ² and all data)	wR2 = 0.0568
Absolute structure parameter	0.015(16)
Extinction coefficient	0.0162(6)
Final maximum delta/sigma	0.001
Weighting scheme	calc $w = 1 / [s^2(F_o^2) + (0.0321P)^2 + 0.1803P]$, where $P = (F_o^2 + 2F_c^2) / 3$
Largest diff. peak and hole	0.205 and -0.116 e.Å ⁻³

PART C Solution and refinement

	x	y	z	U(eq)
C(1)	9(2)	231(1)	5647(2)	29(1)
N(2)	-754(2)	-274(1)	6735(1)	31(1)
S(3)	-1516(1)	-45(1)	9263(1)	38(1)
C(4)	-610(2)	191(1)	7860(2)	30(1)
O(4)	440(2)	941(1)	7767(1)	36(1)
C(5)	1216(2)	878(2)	6502(2)	34(1)
C(6)	-1424(2)	714(1)	4657(2)	31(1)
C(6 ₁)	-1291(3)	1788(2)	4606(2)	39(1)
C(6 ₂)	-3278(2)	479(2)	5012(2)	42(1)
C(7)	-1060(2)	224(2)	3331(2)	35(1)
C(8)	639(2)	573(2)	2813(2)	39(1)
C(9)	2026(2)	173(2)	3843(2)	38(1)
C(10)	956(2)	-436(2)	4751(2)	35(1)
C(11)	-531(3)	-774(2)	3779(2)	39(1)
C(1')	4857(2)	2569(1)	10301(2)	31(1)
N(2')	3713(2)	2934(1)	11282(2)	33(1)
S(3')	3312(1)	2796(1)	13890(1)	42(1)
C(4')	3936(2)	2475(1)	12418(2)	34(1)
O(4')	4826(2)	1677(1)	12262(1)	42(1)
C(5')	5040(3)	1569(2)	10852(2)	40(1)
C(6')	6578(2)	3181(2)	10244(2)	32(1)
C(6 ₁ ')	8256(2)	2635(2)	10625(2)	47(1)
C(6 ₂ ')	6568(3)	4046(2)	11150(2)	42(1)
C(7')	6434(3)	3508(2)	8785(2)	38(1)
C(8')	6734(3)	2692(2)	7839(2)	45(1)
C(9')	5130(3)	2064(2)	7959(2)	46(1)
C(10')	4016(2)	2633(2)	8881(2)	39(1)
C(11')	4470(3)	3646(2)	8511(2)	42(1)

Table 2 Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for oxazolidinethione **145**. $U(\text{eq})$ is defined as one third of the trace of the orthogonalised U_{ij} tensor.

Bond	Length (Å)
C(1)-C(10)	1.535(3)
C(1')-C(10')	1.537(2)
C(1)-C(5)	1.531(2)
C(1')-C(5')	1.527(3)
C(1)-C(6)	1.592(2)
C(1')-C(6')	1.592(2)
C(1)-N(2)	1.475(2)
C(1')-N(2')	1.472(2)
C(10)-C(11)	1.534(3)
C(10')-C(11')	1.533(3)
C(3)-O(4)	1.345(2)
C(3')-O(4')	1.340(2)
C(6)-C(61)	1.528(3)
C(6')-C(61')	1.534(3)
C(6)-C(62)	1.539(2)
C(6')-C(62')	1.533(3)
C(6)-C(7)	1.557(2)
C(6')-C(7')	1.547(3)
C(7)-C(11)	1.534(3)
C(7')-C(11')	1.534(3)
C(7)-C(8)	1.531(3)
C(7')-C(8')	1.532(3)
C(8)-C(9)	1.547(3)
C(8')-C(9')	1.539(3)
C(9)-C(10)	1.546(3)
C(9')-C(10')	1.544(3)
N(2)-C(3)	1.315(2)
N(2')-C(3')	1.323(3)
O(4)-C(5)	1.458(2)
O(4')-C(5')	1.459(2)
S(3)-C(3)	1.664(18)
S(3')-C(3')	1.665(2)

Table 3 Bond lengths (Å) for oxazolidinethione **145**

Bond	Angle (degrees)
N(2)-C(1)-C(5)	97.33(13)
N(2)-C(1)-C(10)	112.17(16)
C(5)-C(1)-C(10)	114.04(14)
N(2)-C(1)-C(6)	112.53(13)
C(5)-C(1)-C(6)	117.74(16)
C(10)-C(1)-C(6)	103.41(14)
C(3)-N(2)-C(1)	113.12(16)
N(2)-C(3)-O(4)	110.39(15)
N(2)-C(3)-S(3)	128.77(15)
O(4)-C(3)-S(3)	120.84(13)
C(3)-O(4)-C(5)	107.61(14)
O(4)-C(5)-C(1)	105.18(13)
C(61)-C(6)-C(62)	106.83(17)
C(61)-C(6)-C(7)	113.49(16)
C(62)-C(6)-C(7)	109.66(16)
C(61)-C(6)-C(1)	113.84(16)
C(62)-C(6)-C(1)	112.02(15)
C(7)-C(6)-C(1)	101.01(14)
C(8)-C(7)-C(11)	100.61(16)
C(8)-C(7)-C(6)	111.46(15)
C(11)-C(7)-C(6)	102.54(15)
C(7)-C(8)-C(9)	102.63(16)
C(10)-C(9)-C(8)	103.47(15)
C(11)-C(10)-C(1)	101.85(14)
C(11)-C(10)-C(9)	101.55(15)
C(1)-C(10)-C(9)	107.86(17)
C(7)-C(11)-C(10)	94.13(16)
N(2')-C(1')-C(5')	97.11(14)
N(2')-C(1')-C(10')	112.25(15)
C(5')-C(1')-C(10')	114.72(17)
N(2')-C(1')-C(6')	112.17(15)
C(5')-C(1')-C(6')	117.66(16)
C(10')-C(1')-C(6')	103.30(14)
C(3')-N(2')-C(1')	111.64(17)
N(2')-C(3')-O(4')	110.36(17)
N(2')-C(3')-S(3')	128.14(16)
O(4')-C(3')-S(3')	121.47(15)
C(3')-O(4')-C(5')	107.49(16)

O(4')-C(5')-C(1')	104.28(16)
C(62')-C(6')-C(61')	107.11(16)
C(62')-C(6')-C(7')	109.26(17)
C(61')-C(6')-C(7')	113.08(15)
C(62')-C(6')-C(1')	111.91(15)
C(61')-C(6')-C(1')	14.10(17)
C(7')-C(6')-C(1')	101.35(14)
C(8')-C(7')-C(11')	100.19(17)
C(8')-C(7')-C(6')	111.65(18)
C(11')-C(7')-C(6')	102.24(15)
C(7')-C(8')-C(9')	103.14(16)
C(8')-C(9')-C(10')	103.51(19)
C(11')-C(10')-C(1')	101.29(16)
C(11')-C(10')-C(9')	101.19(17)
C(1')-C(10')-C(9')	108.69(16)
C(10')-C(11')-C(7')	94.41(17)

Table 4 Bond angles (degrees) for oxazolidinethione **145**

Symmetry transformations used to generate equivalent atoms:

	U11	U22	U33	U23	U13	U12
C(1)	27(1)	30(1)	30(1)	1(1)	1(1)	3(1)
N(2)	34(1)	30(1)	29(1)	1(1)	0(1)	7(1)
S(3)	44(1)	38(1)	33(1)	3(1)	8(1)	3(1)
C(3)	28(1)	29(1)	34(1)	1(1)	1(1)	2(1)
O(4)	39(1)	34(1)	34(1)	4(1)	3(1)	8(1)
C(5)	32(1)	36(1)	32(1)	0(1)	1(1)	7(1)
C(6)	27(1)	34(1)	32(1)	2(1)	2(1)	2(1)
C(61)	44(1)	36(1)	39(1)	4(1)	5(1)	5(1)
C(62)	28(1)	53(1)	45(1)	8(1)	3(1)	1(1)
C(7)	35(1)	40(1)	31(1)	2(1)	1(1)	2(1)
C(8)	43(1)	44(1)	32(1)	3(1)	9(1)	1(1)
C(9)	32(1)	42(1)	39(1)	7(1)	8(1)	1(1)
C(10)	33(1)	33(1)	38(1)	1(1)	2(1)	3(1)
C(11)	41(1)	36(1)	39(1)	7(1)	3(1)	6(1)
C(1')	32(1)	27(1)	35(1)	2(1)	6(1)	1(1)
N(2')	35(1)	28(1)	36(1)	3(1)	8(1)	5(1)
S(3')	54(1)	36(1)	38(1)	5(1)	15(1)	6(1)

C(3')	32(1)	25(1)	44(1)	3(1)	8(1)	1(1)
O(4')	54(1)	29(1)	45(1)	8(1)	15(1)	8(1)
C(5')	48(1)	28(1)	47(1)	2(1)	13(1)	2(1)
C(6')	30(1)	32(1)	34(1)	0(1)	3(1)	1(1)
C(61')	34(1)	54(1)	54(1)	4(1)	0(1)	3(1)
C(62')	45(1)	39(1)	43(1)	8(1)	4(1)	11(1)
C(7')	41(1)	35(1)	38(1)	4(1)	9(1)	1(1)
C(8')	46(1)	54(1)	37(1)	5(1)	9(1)	6(1)
C(9')	52(1)	47(1)	40(1)	11(1)	1(1)	0(1)
C(10')	32(1)	48(1)	36(1)	6(1)	1(1)	0(1)
C(11')	47(1)	46(1)	32(1)	4(1)	2(1)	11(1)

Table 5 Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **145**.
The anisotropic displacement factor exponent takes the form:
 $2\pi^2 [h^2 a^{*2} U_{11} + \dots + 2 h k a^* b^* U_{12}]$

	x	y	z	U(eq)
H(2)	-1480(30)	-720(20)	6630(20)	52(7)
H(5A)	2387	610	6618	40
H(5B)	1286	1502	6095	40
H(61A)	-2137	2030	3936	59
H(61B)	134	1967	4390	59
H(61C)	-1518	2049	5461	59
H(62A)	-3446	709	5895	63
H(62B)	-3448	-199	4983	63
H(62C)	-4110	779	4381	63
H(7)	-2058	240	2660	42
H(8A)	680	1264	2788	47
H(8B)	792	326	1927	47
H(9A)	2879	-211	3415	45
H(9B)	2633	681	4343	45
H(10)	1619	-947	5223	42
H(11A)	-130	-1161	3061	46
H(11B)	-1446	-1103	4216	46
H(2')	3180(30)	3470(20)	11220(20)	46(7)
H(5'1)	4143	1155	10436	48
H(5'2)	6185	1308	10706	48
H(61D)	9248	3019	10438	71
H(61E)	8266	2056	10117	71
H(61F)	8314	2487	11561	71
H(62D)	6616	3842	12066	63
H(62E)	5513	4405	10946	63
H(62F)	7568	4438	11013	63
H(7')	7125	4078	8621	45
H(8'1)	7806	2351	8110	54
H(8'2)	6796	2919	6930	54
H(9'1)	5459	1451	8348	55
H(9'2)	4506	1963	7093	55
H(10')	2761	2484	8790	47
H(11C)	3994	4116	9092	50
H(11D)	4136	3795	7583	50

Table 6 Hydrogen coordinates ($\times 10^4$), and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$), for **145**.

Studies Towards the Synthesis of the Marine Metabolite, Octalactin A

Alison N. Hulme,* Garnet E. Howells

Department of Chemistry, The University of Edinburgh, King's Buildings, West Mains Road,
Edinburgh, EH9 3JJ, UK

Abstract: Studies towards the synthesis of the marine metabolite octalactin A **1**, are described. Key steps in this strategy include an *anti* aldol reaction to set the C₇-C₈ stereochemistry, Horner Wadsworth Emmons coupling to give the trisubstituted *E*-double bond and a novel samarium-mediated cyclisation reaction.

The metabolites octalactin A and B were isolated in 1991 from a marine actinomycete of the genus *Streptomyces*, found on the surface of a gorgonian octacoral.¹ Octalactin A **1** has been shown to have significant *in vitro* cytotoxicity towards both murine melanoma and human colon tumour cell lines (IC₅₀ = 7.2 x 10⁻³ µg/mL and 0.5 µg/mL respectively).¹ Its novel fully saturated eight-membered ring lactone structure has made it the target of a number of recent synthetic studies.^{2,3}

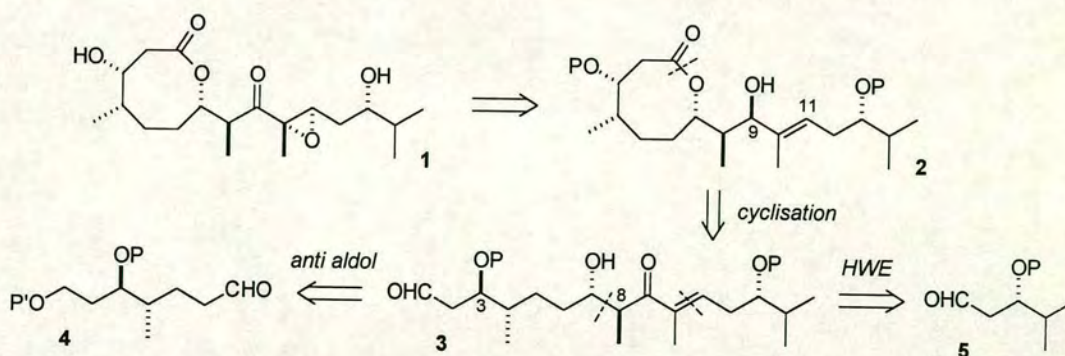
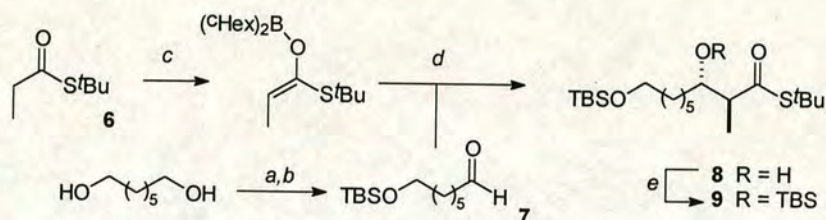


Figure 1

A retrosynthetic analysis of octalactin A is shown in **Figure 1**. Allylic alcohol **2**, a key intermediate, has previously been used to direct introduction of the C₁₀-C₁₁ epoxide,² which is essential for the cytotoxic activity of this metabolite. In contrast to previous syntheses, the novel samarium-mediated cyclisation utilised in

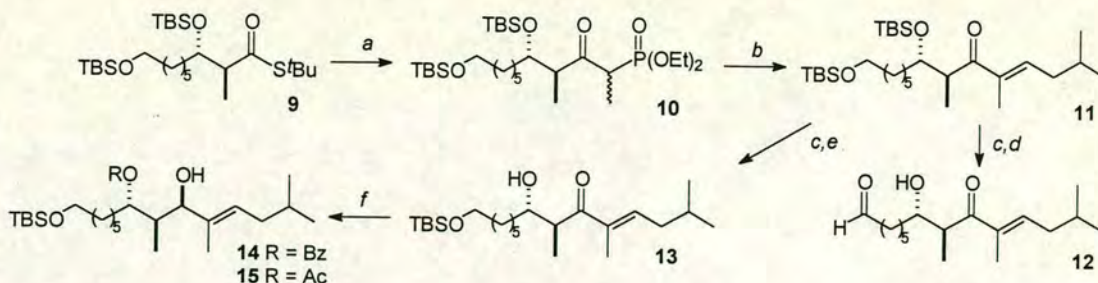
our strategy allows the *stereoselective* generation of the alcohol functionality at C₉. Synthesis of linear precursor **3** was planned from fragments **4** and **5** coupled *via anti* aldol and Horner Wadsworth Emmons reactions to a central five carbon unit. In order to study the cyclisation reaction we used a simple 1,7-difunctional aldehyde in place of the left hand fragment **4**, isovaleraldehyde as a model for aldehyde **5**, and we chose to work on racemic material.

Recent advances in the boron mediated *anti* aldol reaction with thioesters have shown that high levels of both diastereo- and enantioselectivity may be achieved with the appropriate choice of ligand on boron and as a result it has been used successfully in the synthesis of many natural products containing such *anti* stereochemistry.⁴ Enolisation of *t*-butyl thioester **6**⁵ (Et₃N, ^cHex₂BBr) and reaction of the *E*(O)-enol borinate with 1,7-difunctionalised aldehyde **7** resulted in a 79% yield of the aldol adduct **8** with excellent diastereocontrol (>20:1 *anti:syn* as determined by ¹H nmr).⁶ Silyl protection of the β-hydroxy ketone proceeded to give **9** in high yield (93%).



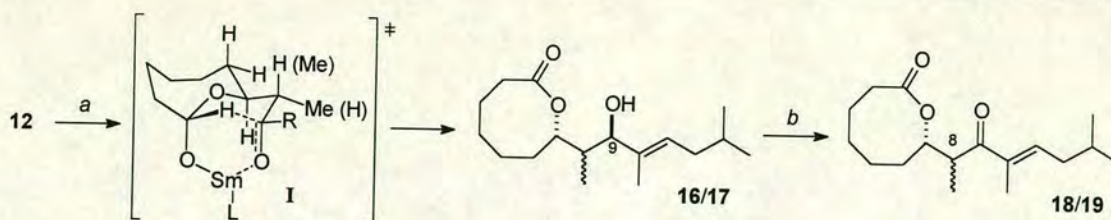
Scheme 1: (a) NaH, THF, rt, 40 min; TBDMSCl, rt, 25 min (82%); (b) IBX, THF/DMSO, rt, 1.5 h (90%); (c) Et₃N, ^cHex₂BBr, Et₂O, 0 °C, 2.5 h; (d) **7**, -78 °C, 25 min; *L*-tartaric acid, -78 °C, 2 h; NaOH, H₂O₂, 2 h (79%);⁷ (e) TBDMSCl, imidazole, DMF, rt, 24 h (93%).

The coupling of a β-keto phosphonate and aldehyde *via* a Horner-Wadsworth-Emmons (HWE) reaction is a much utilised strategy for the formation of *E*-substituted double bonds.⁸ Generation of the phosphonate substrate **10**, for the HWE reaction, was achieved by reaction of the *n*-butyl lithium derived anion of diethylethanephosphonate with protected β-hydroxy thioester **9** (**Scheme 2**).⁹ Under mild HWE coupling conditions (activated Ba(OH)₂, THF(aq.))¹⁰ in the presence of isovaleraldehyde, a high yield of the *E*-trisubstituted alkene **11** was obtained (85%). Subsequent deprotection (HF(aq.), MeCN/THF) and selective TEMPO oxidation¹¹ gave cyclisation precursor **12** (95% over two steps), which was used without further purification due to its instability.



Scheme 2: (a) *n*-BuLi, EtP(O)(OEt)₂, THF, -78 °C, 1 h; 9, -78 °C, 1 h (94%); (b) Ba(OH)₂, THF(aq.), isovaleraldehyde, rt, 6 h (85%); (c) HF (40% aq.), MeCN/THF, 0 °C, 10 min; (d) TEMPO, ^{*n*}Bu₄NCl, NaOCl, NaBr, sat. NaHCO₃ (aq.), sat. NaCl (aq.), CH₂Cl₂, rt, 15 min (95% from 11); (e) TBDMSCl, imidazole, DMF, rt, 4.5 h (85% from 11); (f) PhCHO or MeCHO (4 eq.), SmI₂ (freshly prepared, 1M in THF, 60 mol%) THF, 0 °C, 10 min (70% both).

Recent reports of samarium catalysed cyclisation reactions of keto-aldehyde substrates have focused on the pinacol-based formation of 5- and 6-membered rings.¹² Of these reports, only one has examined the contrasting reactivity of Sm(II) and Sm(III) catalysts, which give rise to pinacol and Tishchenko reactions respectively.^{12c} Tishchenko cyclisation reactions have also been reported using aluminium and lanthanum catalysts.¹³ The Evans-Tishchenko reaction typically requires catalysis by 15-30 mol% of a SmI₂ solution in THF, and results in the directed reduction of a β-hydroxy ketone to give an *anti* diol with selective formation of a monoester (*anti:syn* >95:5).^{14,15} The proposed mechanism invokes intramolecular hydride transfer from an intermediate hemiacetal *via* a transition state similar to **I** (Scheme 3)¹⁴ and is thought to be catalysed by a SmI₃•SmI(RCHO)₂ pinacol adduct which is either preformed, or generated *in situ*. Evans-Tishchenko coupling with either excess benzaldehyde, or acetaldehyde, on protected β-hydroxy enone **13** afforded the *anti* diol monoesters **14** and **15** each in 70% yield as single diastereomers (Scheme 2). To our knowledge, these are the first examples of an Evans-Tishchenko reaction using a β-hydroxy enone, thus considerably extending this methodology. However, when the intramolecular reaction was attempted on **12** using the preformed Sm(III) catalyst (Scheme 3), the formation of a 1:1 ratio of two inseparable diastereomers **16** and **17** was observed (30% combined yield). We believe that an Evans-Tishchenko coupling has occurred to give the lactone, since Tishchenko, or pinacol coupling onto the C₉ carbonyl itself can be excluded on the basis of the ¹H nmr data for the C₇H (δ=4.86-4.81, m) and C₉H (δ=3.88-3.85, 0.5H, m, & δ=3.84-3.91, 0.5H, m), which correlates extremely well with the data for acetate **15**.⁶ A significant change in the chemical shift of the C₁₁ vinylic proton (δ=6.62 ppm (**12**) → δ=5.47 ppm (**16/17**)) also confirmed reduction of the enone functionality.



Scheme 3: (a) PhCHO/SmI₂ (premixed, 0.4M in THF, 30 mol%) THF, 0 °C, 10 min (30%); (b) IBX, THF/DMSO, rt, 2.5 h (82%).

Oxidation of the diastereomeric mixture **16/17** with *o*-iodoxybenzoic acid (IBX) cleanly afforded two diastereomers **18** and **19**, which were now readily separable by chromatography.¹⁶ This indicated that stereoselective hydride transfer had occurred during cyclisation (the *anti* stereochemical assignment at C₉ has been made on the basis of precedent¹⁴) and that loss of stereochemical integrity was perhaps due to epimerisation at C₈ prior to cyclisation.¹⁷ Further evidence for this was found when the ¹H nmr spectrum of the reaction mixture prior to chromatography was examined and it was observed that the unreacted aldehyde **12** was now also a mixture of two diastereomers. Unfortunately, isolation of this unreacted aldehyde was not possible, due to its instability.

With hindsight, our approach to the initial investigation of the construction of the octalactin framework using an unfunctionalised eight membered ring precursor may have required the most demanding mode of cyclisation. In his approach to the octalactins, Andrus has shown that an unfunctionalised C₁-C₉ precursor gives only a 24% yield of the lactone under modified Keck-Boden macrolactonisation conditions, whereas the TBDMS protected, functionalised C₁-C₉ precursor cyclises in 81% yield under the same conditions.^{2a} This has been ascribed to a predisposition of the functionalised substrate to adopt a chair-boat conformation favourable to cyclisation. We are hopeful that fully functionalised precursor **3** will give a similar increase in yield in our cyclisation reaction, and enhance the rate of cyclisation relative to that of competing epimerisation at C₈, (as seen with the reduction of β-hydroxy enone **13**).

We have demonstrated a convergent approach to the carbon framework of octalactin A **1**, which should allow a highly stereocontrolled synthesis of the key intermediate, allylic alcohol **2**. This approach has relied upon a novel samarium-mediated cyclisation strategy. Furthermore, we believe that this synthetic strategy offers an extremely flexible approach towards the synthesis of analogues of the octalactins that may be used to further investigate the structure-activity relationship of this cytotoxic marine metabolite.

Acknowledgements

We thank the EPSRC (GR/95309810 to G.E.H.) and GlaxoWellcome for support. We also thank Miss Rachel H. Walker for initial studies into the *anti* aldol required for the C₇-C₈ bond construction.

References and Notes

1. Tapiolas, D. M.; Roman, M.; Fenical, W.; Stout, T. J.; Clardy, J. *J. Am. Chem. Soc.* **1991**, *113*, 4682-4683.
2. For total synthesis of octalactin A, see: a) Andrus, M. B.; Argade, A. B. *Tetrahedron Lett.* **1996**, *37*, 5049-5052; b) Busek, K. R.; Jeong, Y. *Tetrahedron Lett.* **1995**, *36*, 7189-7192; c) Busek, K. R.; Sato, N.; Jeong, Y. *J. Am. Chem. Soc.* **1994**, *116*, 5511-5512; d) McWilliams, J. C.; Clardy, J. *J. Am. Chem. Soc.* **1994**, *116*, 8378-9379.
3. For other synthetic approaches to the octalactins, see: a) Kodama, M.; Matsushita, M.; Terada, Y.; Takeuchi, A.; Yoshio, S.; Fukuyama, Y. *Chem. Lett.* **1997**, 117-118; b) Bach, J.; Berenguer, R.; Garcia, J.; Vilarrasa, J. *Tetrahedron Lett.* **1995**, *36*, 3425-3428; c) Fuhry, M. A. M.; Holmes, A. B.; Looney, M. G.; Tan, E. *Abstr. Papers, Am. Chem. Soc.* **1994**, *208*, 59 (ORGN).
4. a) Paterson, I.; Hulme, A. N. *J. Org. Chem.* **1995**, *60*, 3288-3300; b) Gennari, C.; Pain, G.; Moresca, D. *J. Org. Chem.* **1995**, *60*, 6248-6249; c) Gennari, C.; Moresca, D.; Vieth, S.; Vulpetti, A. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1618-1621.
5. Schleppnik, A. A.; Zienty, F. B. *J. Org. Chem.* **1964**, *29*, 1910-1915.
6. All new compounds gave spectroscopic data in agreement with the assigned structures: aldehyde **12**: Clear oil; IR (neat) ν_{\max} 3456, 1722, 1655 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) 9.69 (1H, t, *J* = 0.7 Hz), 6.62 (1H, t, *J* = 7.2 Hz), 3.74-3.52 (1H, m), 3.29-3.15 (1H, m), 3.07 (1H, br s), 2.36 (2H, td, *J* = 7.3 & 0.7 Hz), 2.10 (2H, dd_t, *J* = 7.2 Hz), 1.82-1.20 (9H, m), 1.70 (3H, s), 1.09 (3H, d, *J* = 7.3 Hz), 0.88 (6H, d, *J* = 6.6 Hz); ¹³C NMR (50.3 MHz, CDCl₃) 206.4, 201.7, 141.9, 136.4, 72.9, 42.6 (2C), 37.0, 33.6, 27.8, 27.1, 24.4, 21.2 (2C), 20.7, 14.8, 10.2; acetate **15**: Clear oil; IR (neat) ν_{\max} 3456, 1717, 1645 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) 5.44 (1H, t, *J* = 7.4 Hz), 4.79 (1H, dt_q, *J* = 6.4 Hz), 3.90-3.82 (1H, m), 3.55 (2H, t, *J* = 6.2 Hz), 2.03 (3H, s), 1.90 (2H, dd_t, *J* = 7.0 Hz), 1.88-1.72 (1H, m), 1.68-1.18 (11H, m), 1.54 (3H, s), 0.90-0.79 (18H, m), 0.0 (6H, s); ¹³C NMR (50.3 MHz, CDCl₃) 171.3, 135.3, 125.0, 76.0, 75.9, 63.0, 39.0, 36.6, 32.6, 30.6, 29.1, 28.6, 25.8 (3C), 25.5, 25.4, 22.3 (2C), 21.0, 18.2, 12.8, 9.3, -5.5 (2C); *m/z* (FAB) 443 ([M+H]⁺, 1), 425 (10), 364 (31), 73 (100%); HRMS (FAB) Calculated for C₂₅H₅₁O₄Si [M+H]⁺: 443.3557, found: 443.3556; lactones **16/17**: Clear oil; IR (neat) ν_{\max} 3420, 1726 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) 5.47 (1H, tq, *J* = 7.4 & 1.3 Hz), 4.86-4.81 (1H, m), 3.88-3.85 (0.5H, m), 3.84-3.81 (0.5H, m), 2.42-2.27 (2H, m), 2.09 (0.5H, d, *J* = 3.7 Hz), 2.05 (0.5H, d, *J* = 3.7 Hz), 1.93 (2H, dd_t, *J* = 7.4 Hz), 1.88-1.82 (1H, m), 1.81-1.50 (8H, m), 1.40-1.20 (4H, m), 0.90-0.87 (6H, m), 0.82 (1.5H, d, *J* = 7.0 Hz), 0.81 (1.5H, d, *J* = 7.0 Hz); ¹³C NMR (50.3 MHz, CDCl₃) 174.1, 173.8, 135.3, 135.2, 125.0, 124.8, 75.7, 75.6*, 74.7, 38.8*, 36.6*, 33.6, 33.4, 30.5*, 28.6*, 28.5, 28.2, 24.4*, 24.0*, 22.4*, 22.2*, 13.0*, 9.1, 9.0 (*=peaks common to **16** and **17**); *m/z* (FAB) 283 ([M+H]⁺, 2), 265 (20), 55 (100%); HRMS (FAB) Calculated for C₁₇H₃₁O₃ [M+H]⁺: 283.2273, found: 283.2267; enone **18**: Clear oil; IR (neat) ν_{\max} 1726, 1658 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) 6.89 (1H, t, *J* = 7.3 Hz), 5.06-5.00 (1H, m), 3.67 (1H, dq_{qn}, *J* = 6.8 Hz), 2.32-2.22 (2H, m), 2.18 (2H, dd_t, *J* = 7.0 Hz), 1.90-1.75 (1H, m), 1.75 (3H, s), 1.65-1.20 (8H, m), 1.00 (3H, d, *J* = 6.6 Hz), 0.98 (3H, d, *J* = 6.6 Hz), 0.96 (3H, d, *J* = 6.6 Hz); ¹³C NMR (50.3 MHz, CDCl₃) 202.5, 172.8, 142.8, 137.1, 74.5, 41.6, 38.2, 33.8, 28.8, 28.3 (2C), 24.6, 23.8, 22.4 (2C), 11.6, 11.2; *m/z* (FAB) 281 ([M+H]⁺, 7), 263 (4), 125 (44), 92 (100%); enone **19**: Clear oil; IR (neat) ν_{\max} 1731, 1665 cm⁻¹; ¹H NMR (250 MHz, CDCl₃) 6.78 (1H, td, *J* = 7.3 & 1.2 Hz), 5.07-5.01 (1H, m), 3.58 (1H, dq_{qn}, *J* = 7.0 Hz), 2.23 (2H, t, *J* = 6.0 Hz), 2.15 (2H, dd, *J* = 7.3 & 6.6 Hz), 1.84 (1H, spt, *J* = 6.6 Hz), 1.72 (3H, d, *J* = 1.2 Hz), 1.71-1.20 (8H, m), 1.02 (3H, d, *J* = 7.0 Hz), 0.96 (3H, d, *J* = 6.6 Hz), 0.94 (3H, d, *J* = 6.6 Hz); ¹³C NMR (62.9 MHz, CDCl₃) 202.7,

- 172.9, 142.3, 137.2, 75.4, 42.0, 38.2, 33.6, 29.6, 28.6, 28.3, 24.4, 24.2, 22.4 (2C), 12.5, 11.7; m/z (FAB) 281 ($[M+H]^+$, 4), 263 (3), 92 (82), 74 (100%).
7. Low temperature tartrate quench for *anti* aldol reactions: Raimundo, B. C.; Heathcock, C. H. *Synlett* **1995**, 1213-1214.
 8. Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863-927.
 9. In model studies we have performed a number of similar displacement reactions, which will be reported separately.
 10. Paterson, I.; Yeung, K.-S.; Smaill, J. B. *Synlett* **1993**, 744-746.
 11. Siedlecka, R.; Skarzewski, J.; Mlochowski, J. *Tetrahedron Lett.* **1990**, *31*, 2177-2180.
 12. a) Kawatsura, M.; Kishi, E.; Kito, M.; Sakai, T.; Shirahama, H.; Matsuda, F. *Synlett* **1997**, 479-480; b) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307-338 and references cited therein; c) Uenishi, J.; Masuda, S.; Wakabayashi, S. *Tetrahedron Lett.* **1991**, *32*, 5097-5100.
 13. a) Onozawa, S.; Sakakura, T.; Tanaka, M.; Shiro, M. *Tetrahedron* **1996**, *52*, 4291-4302; b) Lange, G. L.; Organ, M. G. *Synlett* **1991**, 665-667.
 14. a) Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1990**, *112*, 6447-6449; b) Romo, D.; Meyer, S. D.; Johnson, D. D.; Schreiber, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 7906-7907.
 15. Similar results have recently been reported for the zirconocene catalysed reduction of β -hydroxy ketones with aldehydes: Umekawa, Y.; Sakaguchi, S.; Nishiyama, Y.; Ishii, Y. *J. Org. Chem.* **1997**, *62*, 3409-3412.
 16. Oxidation of **15** with IBX proceeded cleanly, to regenerate the enone functionality in 84% yield (no epimerisation at C₈).
 17. Similar epimerisation has been observed in a titanium-mediated aldol-Tishchenko reaction: Mahrwald, R.; Costisella, B. *Synthesis* **1996**, 1087-1089.

Synthesis of β -ketophosphonates from Thioester Intermediates: A Stereocontrolled Route to the C₂₉C₃₅ Fragment of the Halichondramides

Alison N. Hulme,* Garnet E. Howells, Rachel H. Walker

Department of Chemistry, The University of Edinburgh, King's Buildings, West Mains Road, Edinburgh, EH9 3JJ, UK

e-mail: Alison.Hulme@ed.ac.uk

Received 13 May 1998

Abstract: An efficient synthesis of β -ketophosphonates from *t*-butyl thioesters using the lithium anion of either methane- or ethane-phosphonate is described. The elaboration of a range of substrates to intermediates in natural product syntheses via the Horner Wadsworth Emmons reaction is then discussed.

In a recent synthesis of a model for the cytotoxic marine metabolite octalactin A 1, we identified a key target 2 (Figure 1).¹ Retrosynthetic analysis of this compound led us to propose a stereocontrolled boron-mediated *anti* aldol between *t*-butyl thiopropionate and a 1,7-difunctional aldehyde to set the C₇–C₈ stereochemistry. We were then faced with the problem of how to extend the carbon backbone of the resultant acyclic β -hydroxy thioester to give enone 3, an advanced precursor to compound 2.

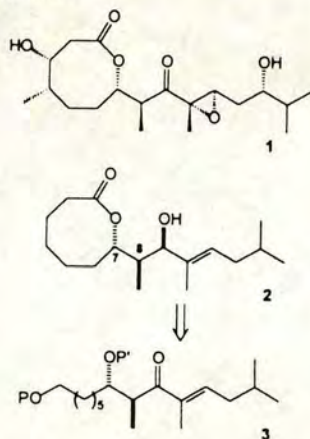


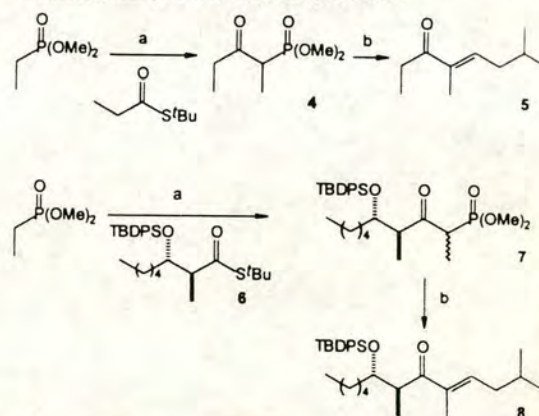
Fig. 1

Thioesters have been used as intermediates in a number of important natural product syntheses. However, their elaboration has largely been limited to the generation of carboxylic acids,² esters,^{2f} lactones,^{2f} aldehydes,^{3a} and β -ketoamides.^{3b} The potential for the use of thioesters in natural product synthesis has greatly increased recently due to a number of developments in aldol methodology, where particularly difficult aspects of stereocontrol have been tackled effectively. Chiral boron reagents developed by Gennari,⁴ and Masamune⁵ have been shown to give high levels of both diastereo- and enantio-control with thioester substrates, resulting in the formation of *anti* aldol adducts in >95% ds and >95% ee. Similarly, in the development of new chiral Lewis acids for the catalytic asymmetric Mukaiyama acetate aldol reaction, many authors have concentrated on the use of thioester substrates.⁶ Thus, new methodology for their synthetic elaboration is particularly important.

The Horner Wadsworth Emmons (HWE) reaction between alkyl phosphonates and aldehydes is frequently used for the synthesis of di- and tri-substituted double bonds.^{7a,b} The development of a number of mild conditions for the HWE reaction between β -ketophosphonates and aldehydes,⁸ makes this reaction particularly suited to the synthesis of

complex natural products, where it has found use both in fragment coupling,⁹ and macrocyclisation reactions.¹⁰ In a recent paper,¹¹ Mosset identified a number of distinct routes to the synthesis of β -ketophosphonates. Of particular relevance to this work is the reaction of α -carbanionic alkylphosphonates with a range of substrates including aldehydes (followed by oxidation),^{11,12} carboxylic acid esters,^{9-11,13} carboxylic acid chlorides,^{11,14} *N*-methoxy-*N*-methylcarboxamides (Weinreb amides),^{11,15} and 3-acylthiazolidine-2-thiones.^{11,16} In this Letter, we report an extension of this strategy to the reaction of α -carbanionic alkylphosphonates with a range of functionalised thioesters.

We found that we could carry out a displacement reaction on *t*-butyl thiopropionate using the lithiated anion of dimethyl ethanephosphonate (Scheme 1), to give the β -ketophosphonate 4 in 76% yield. This was then coupled to isovaleraldehyde using the mild activated barium hydroxide HWE conditions of Paterson,^{8c} to give trisubstituted enone 5,^{7c} also in excellent yield (85%). When the displacement reaction was carried out using the *t*-butyldiphenylsilyl protected *anti* aldol adduct 6,¹⁶ it was similarly successful, generating β -ketophosphonate 7 as a ~3:1 mixture of diastereomers in 73% yield.¹⁷ This could be converted via the HWE reaction to enone 8 in 71% yield without epimerisation of the *anti* stereochemistry derived from the aldol adduct.



Scheme 1. Reagents: a) i. *t*-BuLi, DMPU, THF, -42 °C, 1 h, ii. thioester, -78 °C, 4 h; b) isovaleraldehyde, activated Ba(OH)₂, THF (aq.), rt, 6–8 h

This displacement reaction was then extended to a series of *anti* aldol adducts 9, of the type required for the generation of enone 3 (Table 1).¹⁸ Although these reactions were initially conducted using *t*-BuLi in the presence of DMPU (1 eq.) (Method A), we later discovered that deprotonation by *n*-BuLi was equally effective, and that the addition of DMPU was not required (Method B). In general, the best results were obtained when the solution of the carbanion was added *via* cannula to a precooled solution of the thioester. It was also noted that the anion generated from dimethyl ethanephosphonate was considerably more sluggish in its reactions than its diethyl counterpart and generally required either a higher reaction temperature (-42 °C *cf.* -78 °C), or longer reaction times, for the reaction to proceed to completion.

Table 1

Entry	Method	n	R	R''	P	P'	T	%Yield 10	%Yield HWE
1	A	3	Me	Me	TBS	TBS	-78 °C	69	85
2	B	3	Et	Me	TBS	TBS	-78 °C	85	91
3	B	3	Et	Me	PMB	TBS	-78 °C	86	96
4	B	5	Me	H	TBS	TBS	-78 °C	84	70
5	A	5	Me	Me	TBS	TBDPS	-42 °C	80	82
6	B	5	Et	Me	TBS	TBS	-78 °C	94	85 (3)
7	B	8	Et	Me	TBS	TBS	-78 °C	94	88

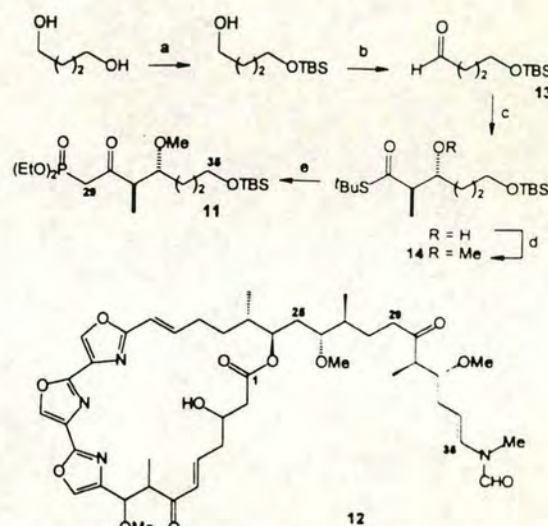
* yield based on unrecovered starting material

Method A: i. *n*-BuLi, DMPU (1 eq.), THF, 1 h; ii. thioester, -78 °C or -42 °C, 4 h; Method B: i. *n*-BuLi, THF, 1 h; ii. add to thioester in THF, -78 °C, 4 h

From these results it can be seen that a range of protecting groups is tolerated by these reaction conditions. Where the lithiated anion of dimethyl methanephosphonate was used to generate β -ketophosphonate 10, a di-substituted double bond was generated by the HWE reaction (Entry 4). The *E*-geometry of this double bond was confirmed by the ^1H nmr coupling constant ($J = 15.8$ Hz). As with aldol adduct 6, the reactions of dialkyl ethanephosphonate anions with aldol adducts 9 were found to produce a ~3:1 ratio of diastereomers 10, which were converted to a single *E*-double bond geometry in the HWE reaction.^{7c}

We have used these conditions in the synthesis of enone 3 ($P=P'=TBS$, Entry 6) which has subsequently been used in the construction of key target 2.¹ In order to demonstrate the general applicability of this protocol we also chose to synthesise β -ketophosphonate 11, which has been used by Pattenden as the C_{29} , C_{35} section of the halichondramide backbone (12, Scheme 2).^{9d} Aldehyde 13 was generated through monoprotection of butane-1,4-diol as its *t*-butyldimethylsilyl ether,¹⁹ followed by oxidation by *o*-iodoxybenzoic acid. Enolisation of *t*-butyl thiopropionate with Et_3N and $^t\text{Hex}_2\text{BBr}$ and reaction with aldehyde 13 generated the *anti* aldol adduct in 81% yield as a single diastereomer. Subsequent methylation of the free hydroxyl was achieved using Meerwein's salt in the presence of Proton-Sponge[®] (Aldrich) to give protected thioester 14. Phosphonate displacement was carried out using two equivalents of the anion following the protocol described in Method B.¹⁸ A previously unobserved minor impurity, formed by elimination of methanol from β -ketophosphonate 11, was noted in the ^1H nmr of the crude reaction mixture. However, this impurity was found to be readily separable by HPLC allowing the isolation of 11 in 64% yield.²⁰ Thus the synthesis was successfully completed giving (\pm)-11 in 5 steps with an overall yield of 38%, which compares extremely favourably with the earlier synthesis.

In conclusion, we have developed an efficient route for the conversion of functionalised thioesters to β -ketophosphonates and we have demonstrated the addition of these β -ketophosphonates to aldehydes under mild Horner Wadsworth Emmons reaction conditions. This protocol considerably extends the options available for the elaboration of thioesters in natural product synthesis, as demonstrated by the synthesis of enone 3 and β -ketophosphonate 11.



Scheme 2. Reagents: a) i. NaH, THF, rt, 40 min; ii. TBDMSCl, rt, 1 h (89%); b) *o*-iodoxybenzoic acid (IBX), DMSO/THF, rt, 1 h (88%); c) i. *t*-butyl thiopropionate, $^t\text{Hex}_2\text{BBr}$, Et_3N , 0 °C, 2 h; ii. aldehyde 13, 0 °C, 2 h (81%); d) Me_3OBF_4 , Proton-Sponge[®], 0 °C, 2 h (94%); e) i. $(\text{EtO})_2\text{P}(\text{O})\text{Me}$, *n*-BuLi, THF, -78 °C, 1 h; ii. thioester 14, -78 °C, 1 h (64%)

Acknowledgements. We thank the EPSRC (GR95309810 to G.E.H.), The University of Edinburgh (Vacation Scholarship to R.H.W.), The Royal Society and GlaxoWellcome for the support of this work.

References and Notes

- Hulme, A. N.; Howells, G. E. *Tetrahedron Lett.* **1997**, 38, 8245-8248.
- a) Gennari, C.; Pain, G.; Moresca, D. *J. Org. Chem.* **1995**, 60, 6248-6249; b) Paterson, I.; Hulme, A. N. *J. Org. Chem.* **1995**, 60, 3288-3300; c) Chamberlin, A. R.; Dezube, M.; Reich, S. H.; Sall, D. J. *J. Am. Chem. Soc.* **1989**, 111, 6247-6256; d) Masamune, S.; Lu, L. D.-L.; Jackson, W. P.; Kaiho, T.; Toyoda, T. *J. Am. Chem. Soc.* **1982**, 104, 5523-5526; e) Kaiho, T.; Masamune, S.; Toyoda,

- T. *J. Org. Chem.* **1982**, *47*, 1612-1614; f) Masamune, S. *Aldrichimica Acta* **1978**, *11*, 23-32 and references cited therein.
- 3 a) Fukuyama, T.; Lin, S.-C.; Li, L. *J. Am. Chem. Soc.* **1990**, *112*, 7050-7051; b) Ley, S. V.; Smith, S. C.; Woodward, P. R. *Tetrahedron* **1992**, *48*, 1145-1174.
 - 4 Gennari, C.; Moresca, D.; Vieth, S.; Vulpetti, A. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1618-1621.
 - 5 Masamune, S.; Sato, T.; Kim, B.M. Wollmann, T. A. *J. Am. Chem. Soc.* **1986**, *108*, 8279-8281.
 - 6 a) Review: Mukaiyama, T. *Aldrichimica Acta* **1996**, *29*, 59-76; b) Keck, G. E.; Krishnamurthy, D. *J. Am. Chem. Soc.* **1995**, *117*, 2363-2364; c) Review: Bach, T. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 417-419.
 - 7 Reviews: a) Nicolaou, K. C.; Harter, M. W.; Gunzner, J. L.; Nadin, A. *Liebigs Ann. Rec.* **1997**, 1283-1301; b) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863-927; c) *E-alkene geometry assigned on the basis of literature precedent.*
 - 8 a) Rubsam, F.; Evers, A. M.; Michel, C.; Giannis, A. *Tetrahedron* **1997**, *53*, 1707-1714; b) Bonadies, F.; Cardilli, A.; Lattanzi, A.; Orelli, L. R.; Scettri, A. *Tetrahedron Lett.* **1994**, *35*, 3383-3386; c) Paterson, I.; Yeung, K.-S.; Smaill, J. B. *Synlett* **1993**, 774-776; d) Koskinen, A. M. P.; Koskinen, P. M. *Synlett* **1993**, 501-502.
 - 9 For recent examples, see: a) Mulzer, J.; Berger, M. *Tetrahedron Lett.* **1998**, *39*, 803-808; b) Nakada, M.; Kobayashi, S.; Iwasaki, S.; Ohno, M. *Tetrahedron Lett.* **1993**, *34*, 1035-1038; c) Boger, D. L.; Curran, T. T. *J. Org. Chem.* **1992**, *57*, 2235-2244; d) Kiefel, M. J.; Maddock, J.; Pattenden, G. *Tetrahedron Lett.* **1992**, *33*, 3227-3230; e) Han, Q.; Wiemer, D. F. *J. Am. Chem. Soc.* **1992**, *114*, 7692-7697; f) Hoffmann, R. W.; Ditrach, K. *Liebigs Ann. Chem.* **1990**, 23-29.
 - 10 For recent examples, see: a) Stocksdales, M. G.; Ramurthy, S.; Miller, M. J. *J. Org. Chem.* **1998**, *63*, 1221-1225; b) Astles, P. C.; Thomas, E. J. *J. Chem. Soc., Perkin Trans. I* **1997**, 845-856; c) Johnson, C. R.; Zhang, B. R. *Abstr. Papers, Am. Chem. Soc.* **1996**, *211*, 125 (ORGN); d) Marshall, J. A.; DuBay, W. J. *J. Org. Chem.* **1994**, *59*, 1703-1708; e) Roush, W. R.; Warmus, J. S.; Works, A. B. *Tetrahedron Lett.* **1993**, *34*, 4427-4430.
 - 11 Delamarche, I.; Mosset, P. *J. Org. Chem.* **1994**, *59*, 5453-5457, and references cited therein.
 - 12 a) Pipelier, M.; Ermolenko, M. S.; Zampella, A.; Olesker, A.; Lukacs, G. *Synlett* **1996**, 24-26; b) Paterson, I.; Yeung, K.-S.; *Tetrahedron Lett.* **1993**, *34*, 5347-5350.
 - 13 a) Deziel, R.; Plante, R.; Caron, V.; Grenier, L.; Llinas-Brunet, M.; Duceppe, J. S.; Malenfant, E.; Moss, N. *J. Org. Chem.* **1996**, *61*, 2901-2903; b) Neidlen, R.; Feistauer, H. *Helv. Chim. Acta* **1996**, *79*, 895-913; c) Konoike, T.; Araki, Y. *J. Org. Chem.* **1994**, *59*, 7849-7854; d) Mulzer, J.; List, B. *Tetrahedron Lett.* **1994**, *35*, 9021-9024.
 - 14 a) Takemoto, M.; Koshida, A.; Miyazima, K.; Suzuki, K.; Achiwa, K. *Chem. Pharm. Bull.* **1991**, *39*, 1106-1111; b) Kuo, F.; Fuchs, P. L. *Synth. Commun.* **1986**, *16*, 1745-1759; c) Honda, M.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1984**, *35*, 3857-3860.
 - 15 a) Blackwell, C. M.; Davidson, A. H.; Launchbury, S. B.; Lewis, C. N.; Morrice, E. M.; Reeve, M. M.; Roffey, J. A. R.; Tipping, A. S.; Todd, R. S. *J. Org. Chem.* **1992**, *57*, 1935-1937; b) Dufour, M. N.; Jouin, P.; Poncet, J.; Pantaloni, A.; Castro, B. *J. Chem. Soc. Perkin Trans. I* **1986**, 1895-1900.
 - 16 Aldol adduct **6** was prepared in two steps from *t*-butyl thiopropionate and hexanal, as shown below:

a) i. LDA, -78 °C, 1 h; TMSCl, -78 °C → rt, 1 h; ii. hexanal, BF₃·OEt₂, -78 °C, 1 h (86%); b) TBDPSCl, DMF, imidazole, rt, 24 h (77%)
 - 17 In this and subsequent reactions, the relative stereochemistry α to the phosphonate was not determined.
 - 18 Typical procedure for Method B: to a solution of diethyl ethanephosphonate (5.84 g, 35.11 mmol) in THF (20 ml) was added *n*-BuLi (1.54 M solution in hexanes, 22.80 ml, 35.11 mmol) dropwise at -78 °C under an atmosphere of argon. After stirring for 50 min at -78 °C the light yellow solution was transferred via cannula into a solution of thioester **9** (Entry 6, 4.02 g, 7.98 mmol) in THF (15 ml) at -78 °C and the resulting solution was stirred for a further 50 min before carefully pouring onto a saturated aqueous solution of NH₄Cl (150 ml). The mixture was extracted with CH₂Cl₂, washed with brine, dried (MgSO₄) and the volatiles removed under reduced pressure. Purification of the crude material by flash chromatography with hexane/EtOAc (3:2) as eluent afforded the β -ketophosphonate **10** (Entry 6) as a clear oil 4.23 g (94%).
10 (P=P'=TBS, *n*=5), 3.3:1 mixture of diastereomers: IR (neat) 1712, 1251 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) 4.26-4.06 (4H, m, P(OCH₂CH₃)₂), 4.02-3.95 (0.23H, m, CHOTBS), 3.94-3.84 (0.77H, m, CHOTBS), 3.63 (2H, t, *J* = 6.4 Hz, CH₂OTBS), 3.55-2.98 (2H, m, CHC(O) and CHP(O)), 1.65-1.20 (13H, m, CH₂ x 5, CH(CH₃)P(O)), 1.37 (6H, t, *J* = 7.1 Hz, CH₂CH₃ x 2), 1.15 (0.7H, d, *J* = 7.3 Hz, CH(OTBS)CHCH₃), 1.02 (2.3H, d, *J* = 6.6 Hz, CH(OTBS)CHCH₃), 0.93 (9H, s, C(CH₃)₃), 0.90 (2.1H, s, C(CH₃)₃), 0.89 (6.9H, s, C(CH₃)₃), 0.08 (6H, s, SiCH₃), 0.07 (3.7H, SiCH₃), 0.00 (2.3H, SiCH₃); ¹³C NMR (62.9 MHz, CDCl₃) major diastereomer 209.1 (d, ²*J*_{P-C} = 3.6 Hz), 74.7, 63.07, 62.3 (2C, d, ²*J*_{P-C} = 6.7 Hz), 50.7, 48.2 (d, ¹*J*_{P-C} = 25.5 Hz), 33.4, 32.7, 29.6, 25.9 (3C), 25.8, 25.7 (3C), 22.8, 18.2, 17.8, 16.2 (2C), 12.4, 10.4 (d, ²*J*_{P-C} = 5.7 Hz), -4.5, -4.8, -5.4 (2C), minor diastereomer 208.9 (d, ²*J*_{P-C} = 4.5 Hz), 73.1, 63.14, 62.3 (2C, d, ²*J*_{P-C} = 6.7 Hz), 50.3, 45.0 (d, ¹*J*_{P-C} = 28.6 Hz), 33.4, 32.7, 29.6, 25.9 (3C), 25.8, 25.7 (3C), 24.5, 18.2, 17.9, 16.2 (2C), 12.3, 11.4 (d, ²*J*_{P-C} = 6.9 Hz), -4.7, -4.8, -5.4 (2C); FABMS 581 (24%, [M+H]⁺), 523 (100), 449 (78), 279 (99).
 - 19 McDougal, P. G.; Rico, J. G.; Oh, Y.-I.; Condon, B. D. *J. Org. Chem.* **1986**, *51*, 3388-3390.
 - 20 We are grateful to Prof. Pattenden for supplying spectral data for **11**, which was found to be in good agreement with our own data.

ABBREVIATIONS

Ac	acetyl
AcOH	acetic acid
app	apparent
aq	aqueous
Ar	aryl
Bn	benzyl
Bu	butyl
CI	chemical ionisation
^c Hex	cyclohexyl
^c Pen	cyclopentyl
DCC	dicyclohexyl carbodiimide
DET	diethyl tartrate
DIBAL	diisobutylaluminium hydride
DMF	<i>N,N</i> -dimethylformamide
DMAP	4-dimethylaminopyridine
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1 <i>H</i>)-pyrimidinone
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
ds	diastereoselectivity
ee	enantiomeric excess (<i>i.e.</i> % of major enantiomer - % of minor diastereomer)
EI	electron impact ionisation
Et	ethyl
ether	diethyl ether
FAB	fast atom bombardment
HiR _f	high R _f
hfc	3-(heptafluoropropylhydroxymethylene)-(+)-camphorate
HMDS	hexamethyldisilazide
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrum
IBX	iodoxybenzoic acid
IR	infra reds
L	unspecified ligand
LDA	lithium diisopropylamide

LoR _f	low R _f
NOE	nuclear Overhauser effect
M	unspecified metal
<i>M</i>	mol dm ⁻³
Me	methyl
Mes	mesityl
MTPA	methoxytrifluoromethylphenylacetic acid
Nu ⁻	unspecified nucleophile
P	unspecified protecting group
PMB	paramethoxybenzyl
Pr	propyl
ppm	parts per million
Pyr	pyridine
R _t	retention time for HPLC
sat.	saturated
Tf, triflate	trifluoromethanesulphonate
TBAF	tetrabutylammonium fluoride
TBS	<i>t</i> -butyldimethylsilyl
TBDPS	<i>t</i> -butyldiphenylsilyl
TES	triethylsilyl
tlc	thin layer chromatography
TMS	trimethylsilyl
THF	tetrahydrofuran
TMS	trimethylsilyl
Ts	toluenesulphonate
TS	transition state
TFA	trifluoroacetic acid
X	unspecified hetero atom